JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY

&

QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

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QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

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PART I

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JANUARY–MARCH 1956

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Physiodynamic and pharmacodynamic research has given new perspectives to psychiatrists and new hope to patients with mental diseases. The ataractic agent, Miltown (2-methyl-2-*n*-propyl-1-1,3-propanediol dicarbamate), is the latest in a series of new compounds which have already proved to be of great value in clinical practice.

We are pleased to present the original report on meprobamate (Miltown) by the late Dr. Lowell Selling on page 7. This paper not only has an important clinical value but is also of notable historical interest.

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Clinical Psychopathologic Conferences are included as a regular feature of J.C.E.P. This section will attempt to further the attainment of more uniform clinical diagnostic evaluations which is so essential to the elucidation of correlations and associations between clinical, neurologic, psychologic, and biologic elements. Subsequent issues will present clinical case presentations illustrative of other psychophysiopathologic disorders. These will be contributed by psychiatric hospitals, clinics, and psychiatrists throughout the world. Manuscripts together with accompanying illustrations should be forwarded to the JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY, 30 East 60th Street, New York, N. Y., Attention: Editor, Clinical Psychopathologic Conferences.

Due to the unusual length of this issue of the journal, the Clinical Psychopathologic Conference is omitted. This section will appear in future issues.

JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY
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*

The Great Physiodynamic Therapies in Psychiatry*

Félix Martí-Ibáñez, M.D., Arthur M. Sackler, M.D., Mortimer D. Sackler, M.D., and Raymond R. Sackler, M.D.

THE VAN OPHUIJSEN CENTER
NEW YORK, N. Y.

I

In the panorama of man the place of the mentally ill was for centuries determined primarily by the traditional prejudices of society toward the misunderstood sufferings of those it termed "insane." Psychiatric therapy, its history, and its present status also reflect society's attitude toward the psychiatric patient. And now as psychiatry evolves toward a more mature biologic science, it is seen more clearly to follow the historic course of its sister sciences.

In man's earlier days the mentally ill were deemed possessed and, in some later societies, even criminals. The disorder was often held to be either possession by devils or a divine punishment. The predominance of therapeutic nihilism was therefore inevitable. Since there was no recognition of illness, there was no attempt to cure it. Confronted with the incomprehensible behavior of the mentally sick, society reacted by adopting self-protective measures.

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* Foreword to the book, *The Great Physiodynamic Therapies in Psychiatry*, by Drs. Arthur, Mortimer, and Raymond Sackler, and Félix Martí-Ibáñez, with the personal contributions of Drs. Ugo Cerletti, Roy G. Hoskins, L. J. Meduna, Egas Moniz, and Manfred Sakel, to be published by Paul B. Hoeber, Inc., Medical Division of Harper & Bros., in the Spring of 1956.

The institutional period was the first phase of society's approach to management of the mentally sick. The "insane" member, after an attempt at exorcism or punishment for his "crime" by chastisement, was confined. Unhappily, the vast walled communities and mammoth window-barred buildings of this our "enlightened" age are vestiges of the first phase—the removal of the mentally deranged from the society of their fellow men.

Incipit vita nova. Then, like the dawn of a new era in Dante's poem, came the day when the mentally ill were recognized as sick, and the concept of guilt and of antisocial danger began to be rejected and the stigma of "insanity" to recede. Confinement as a therapeutic measure gained a new aim—to protect the patient from himself, to isolate him from some of the emotional stimuli believed responsible for his disorder and from situations with which he could not cope. The beginnings of modern drug therapy wrought further changes by adding to the primitive physical methods, first, pharmacologically induced isolation by sedation and, later, physiodynamically active modalities—insulin, electroconvulsive therapy, metrazol, hormones, and histamine.

More recently, pharmacotherapy has come to the fore with narcobiotic drugs developed through German and Swiss research in artificial hibernation. In France, Laborit combined the use of refrigeration and drugs and opened the way for clinical attempts to reduce the reaction of the neurovegetative system to the effects of homeostatic-disruptive forces. The internal environment was "chemically isolated" from the external environment and, in fact, from the possible aggression of other endogenous psychogenic or metabolic elements.

Historically, *isolation,* accomplished by sedation through physical means and drugs, was followed by the *seismotherapeutic* stage or treatment by means of shock techniques, firstly empirical *pyretotherapy* by *chemical methods, malariotherapy,* and the use of the various agents that provoke convulsions and coma.

Philosophically, shock therapy can be viewed as an attempt to stimulate active defense of the organism to resist disorganizing forces, while the recent use of ataractic drugs attempts to foster passive "defense through submission."

The seismotherapeutic approach (the shock therapy era that bridged the early and the recent pharmacotherapies) can be viewed as being based on "defense through physiologic reorganization" of the organism's metabolism. Although the physiodynamic techniques evolved empirically, we hold that they are destined to lead us to the fundamental etiology and pathogenesis of mental disorders, to a "new" science of psychiatry based on a metabolic understanding of chemical dysequilibrations.

The physiodynamic therapies, as well as the more recent pharmacotherapies, should in turn lead to studies of neuroendocrine and other metabolic alterations produced by these procedures. We may thus advance from empiric therapeutic benefit to a clearer understanding of the metabolic processes that mediate them and to the ultimate biochemical deviations out of which the disease process arises.

II

Psychiatry in the twentieth century started with Kraepelin's interest in the disease entity —in the psychiatric *nosos.* This was followed by the post-Kraepelinian curiosity as to the

semeios or symptoms as exemplified by Freud's already classic concepts in the psychodynamics of symptom formation. The current trend of psychiatric investigation is to search for the *aitia*—for out of understanding the cause will come not only more basic psychiatric nosology but the most definitive measures for the control of mental illness.

The search for the *aitia* will be hastened by a physiodynamic philosophy and perspective. Mental disease cannot exist without an organic structure whose function is disrupted, and this dysfunction derives from metabolic alterations (psychogenic or pathophysiologic in origin) which can affect not only structure but also function. The mind itself has no possible existence other than as an *expression* of the activity of the brain. Physiodynamic psychiatry must accept the fact that psychoses and other mental disorders cannot exist except as they are related to metabolic disturbances operating within organic structures regardless of the origin of the disturbing forces.

In this day of psychosis-inducing chemicals and of drugs capable of "curing" such artificially induced syndromes, it is difficult to conceive of the struggle during the past decade, particularly in the United States, to strengthen and forward a biologic orientation. Kraepelin's clinical intuitions and the isolated but lucid comments of Bleuler and Freud on the biologic roots of psychiatry were for decades overwhelmed and submerged by a wave of "scientific" quasi mysticism. This then led to distortion of the originally brilliant concepts of the dynamics of symptom formation into etiologic forces. Talk superseded basic research, and unsupported hypotheses were propounded as dogma. The defects of nineteenth century psychiatry, in which the systematizing philosophy was based on the work of alienists in mental asylums whose observation material was largely restricted to severe psychoses in the later stages, were replaced by the weaknesses of early twentieth century psychiatry. Then, too many ideas were predicated on the subtle theoretical disquisition of psychotherapists whose experience for the most part was limited to nonhospitalized "neurotics."

The somatotherapies brought a healthy naturalistic trend. Studies began to bridge between hospitalized and nonhospitalized patients. Fundamental criteria for diagnosis, therapy, and signs of improvement began to make their appearance. The challenging chasm between the results attained with the somatotherapies and our lack of knowledge as to how these came about led some investigators to intensify biologic research in psychiatry. Weakness was turned into an advantage, just as the carpenter in the old fable converted his proud sword into a useful saw when its edge had become jagged.

Present-day search for the cause of disease or *aitia* will integrate Kraepelin's interest in the idea of the disease or psychiatric *nosos* and post-Kraepelinian curiosity as to the *semeios* or psychiatric symptoms. Such transition from the nosologic criterium to the symptomatological and, finally, to the etiologic criterium, repeats once more in psychiatry that inevitable historical evolution which has occurred in all branches of scientific medicine.

III

It is of significance, of course, to know who is the father of any important discovery,

but in the spirit of strict justice it is of equal interest to know who is the mother and who the obstetrician that assisted in bringing it forth into the world.

It happens with scientific discoveries, as with literary discoveries, that once the umbilical cord joining them with the mind of their creator is cut, they cease to belong to one person, and they take on a life of their own, ready to grow and change. The original and true features can then be appreciated only if we look at their reflection in the mirror of their creator's own mind.

How instructive it would be, for instance, if the great figures of the past in psychiatry could tell us what they think of their own discoveries re-evaluated in the light of our present-day knowledge! What a lesson in humility and tolerance it would be for many "Freudian" dogmatists if Freud himself were to give us a new estimation of his psychoanalytical theories in the light of the new biologic signposts in psychiatry!

Such is the experiment, unprecedented in the annals of the history of medicine, undertaken by the organizers and editors of this symposium. The great somatotherapies in psychiatry were selected: insulin shock therapy, metrazol shock, electroshock, prolonged sleep therapy,* psychosurgery, and hormonal therapy; and their chief protagonists† were asked to tell simply the circumstances leading to discovery or orientation, and to examine the latter in the light of present-day psychiatric knowledge so as to give it a current evaluation.

Each one of the contributors was invited to relate the historical development of the method associated with his work, its evolution, and the opinion that he himself places on it at the present time, some years after its introduction. Their answers will be found in the ensuing pages, in which is assembled a quarter of a century's labor in tracing distinctive features on the vast mural of contemporary psychiatric knowledge.

These reappraisals take us back to the original fountainhead whence these discoveries sprang, for the somatotherapies nowadays are like transparent glass vessels that take on the color of the liquid contained in them. In the hands of certain psychiatrists these techniques were a prelude to psychotherapy; for others they represented the best physical means of breaking down the vicious circle of certain psychoses; while for the remainder they constituted the best clinical means of treating psychoses.

The physiodynamic therapies are now a basic element in the therapeutic arsenal of the psychiatrist. But, though he may be thoroughly acquainted with the correct ways of using such techniques, it is a rare psychiatrist who has had the time and opportunity to study their origin, development, and comparative value, and to integrate them philosophically into the present psychiatric panorama as a whole in order to evaluate correctly their future possibilities in psychiatry.

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* Unfortunately, ill health prevented Klaesi from submitting his reappraisal of the prolonged sleep therapy, the historical roots of which go back as far as the sixth century when Alexander of Tralles recommended the sleep cure as a remedy against insanity. We have every hope that the absence of so valuable a paper will be remedied in some future edition, since no review of the somatotherapies would be complete without a survey of this important technique, so much in use nowadays in several countries, which is credited with a vast wealth of successful statistics.

† Ugo Cerletti, Roy G. Hoskins, L. J. Meduna, Egas Moniz, and Manfred Sakel.

Only by listening to the words of the original protagonists of these methods can we trace their true historical roots and learn exactly what the original worker was after. To drive home the drama of such a historical lesson, it is necessary to confront the author with his work, the discoverer with his discovery, and thus have an opportunity of evaluating afresh in the light of present-day knowledge what these methods may stand for in the psychiatry of the future.

The men assembled between the covers of this volume do not breathe in an atmosphere of Olympian detachment and infallibility. The reader will observe discrepancies and contradictions here and there among them. We have no qualms in this respect.

The good of humanity has been forwarded by each one of them; a common eagerness for research made them orient their thought navigation into uncharted seas of scientific investigation, and a common success has crowned their endeavors. Each and every one of them submits himself to the historic test of confronting his own work in retrospect, which is a prophylaxis against the danger of dogmatism, that ever-present insidious enemy and camp-follower of science. If we all learned, as Osler suggested, how to die each night in order to be resurrected the next morning, to make a daily reappraisal of the merits and value of our thoughts and work, modern psychiatry would be liberated from the perilous burden of dogmatism which still clogs its progress.

From the contrast between what the physiodynamic therapies actually are in the crucible of daily psychiatric practice and what they are in the ideal image that exists in the mind of their discoverers, the present symposium derives its striking and tellingly personal values. In addition to enlightenment on the historical facts of the past, it provides a hopeful prospection toward the future.

IV

It is essential *to know* if we are *to cure*. In the past, empiric therapy predominated over diagnostic classification. Today, we acknowledge that every medical or psychiatric action entails a feat of cognition as well as of conation. Therefore, in the personality of the psychiatrist, clinical intuition must coexist with both naturalism and criticism. These facets must be combined into that "attitude of scientific expectancy" in the presence of facts which Pavlov, the physiologist and one of the great founders of modern psychiatry, with Kraepelin, the nosologist, Cajal, the anatomist, and Freud, the psychodynamicist, professed and demanded.

The psychiatrist, like the general practitioner, must be, first of all, a naturalist capable of observing with the eyes of a true investigator the signs that nature places before him in the form of the suffering of the sick person. He must learn to observe before trying to experiment, for it is in the careful observation of nature and in the correct interpretation of what nature offers that he will find the most fertile source of scientific progress.

The psychiatrist, however, much more than any other physician, must admit the importance of doubt and of constructive criticism as effective tools with which to carve out new concepts in his field and to smooth the rough edges of the structure he seeks to create. He must not accept a semblance of pathologic fact at its face value; he must learn how to penetrate its façade which may be deceptive; he must reach the true, deep causes of what he observes on the surface.

Since the best way to appreciate a picture properly is to place it in its proper setting, it was deemed helpful to begin this symposium with an historical introduction relating the evolution of the organicist philosophy that through the somatotherapy techniques culminates in physiodynamic psychiatry, and to end it with a chapter tracing the future course of modern psychiatric trends, integrating these somatotechniques into the endless scientific progress of psychiatry. To reminiscence we have added prospection.

Fame has crowned the writers we have collected here for their effort, their tenacity, and their achievements. As to determining the niceties of historical priorities, that is the mission of the historian, who must not allow an obsession with chronologic sequence to blind him to the fact that in medicine, as in all aspects of life, "no man is an island," and that no discovery exists that is not bound both in time and space to the toils and achievements of many who have gone before, often in other times and other lands.

To the merely chronologic fame of a discoverer must be added the truly historical glory of being the first to gather together in his hands the many threads of medical knowledge with which to weave the unique pattern of his contribution. Such renown is not merely a reinvigoration of the past but a dynamic prelude to the future, and that is what true fame is. A fame whose green laurels are represented by the gratitude of the mentally sick to the men who devote their lives and genius to their treatment. To all such men this volume renders the best possible homage—it is a living pedestal to their collective work.

Claude Bernard once said: "*L'art c'est moi; la science c'est nous.*" To that *we*, the stuff of which science is made, this book is respectfully dedicated.

Editor's Note: *The Great Physiodynamic Therapies in Psychiatry* will be published by Paul B. Hoeber, Inc., Medical Division of Harper & Bros., in the Spring of 1956. The preceding paper comprises the foreword to the book.

A Clinical Study of Miltown®, A New Tranquilizing Agent

*Lowell S. Selling, M.D., Ph.D., Dr. P. H., F.A.C.P.**

ORLANDO, FLORIDA

INTRODUCTION

Anxiety neuroses and tension states are so widespread in our time and so distressing to the patient that there is a real need for rapid therapy to relieve the patient and enable him to recover. Attempts to find useful drugs for the relief of anxiety and tension states are being made constantly, and among the more promising of these have been the propanediol preparations developed by Berger.[1–3]

Studies of mephenesin (3-ortho-toloxy-1,2-propanediol), the first propanediol preparation to appear in the medical literature, suggested that manifestations of tension states and other psychoneurotic conditions could be chemically relieved.[4] But the medication was not consistent in its activity; frequently it failed to produce any effect at all. The second propanediol compound to appear was 2,2-diethyl-1,3-propanediol (DEP), which showed much more promise.[5] It was consistent in its control of manifestations of tension states, but its duration of action was too short, about two to three hours, and large doses were required to produce a satisfactory result.

The most recent product of this type, 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate, Miltown,®† is the subject of this study. The pharmacologic investigation of the new tranquilizer has been done by Berger and his associates.[1–3, 6] They conclude that the drug affects the central nervous system by a blocking action on interneurons. In the spinal cord, it shows a mephenesin-like action, but of much longer duration, that relaxes skeletal muscle. In the brain, it has a profound effect on subcortical structures, and particularly on the thalamus. The cortex is affected to a lesser extent. Meprobamate also has a strong anticonvulsant action, protecting mice against the tonic extensor component of maximal electroshock seizures, and especially against metrazol-induced seizures.

Monkeys, after meprobamate administration, lose their fear and hostility, become more manageable, and accept handling and offered food.

Toxicity of the drug was found to be very low. Both acute and chronic studies showed no abnormalities produced in blood, liver, or kidney functions.

PROCEDURE

Patient Selection. The present study covers patients seen in private practice between

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* Deceased. This paper was edited posthumously by Dr. F. M. Berger and Dr. Mortimer D. Sackler.

† Ed. note: The generic name "meprobamate" was given the drug only several months after Dr. Selling's death in January, 1955; the experimental name "Miltown" has, therefore, been retained in the title.

The trade name of Wallace Laboratories for meprobamate is Miltown.

January 15, 1953, and April 1, 1954. All cases were examined physically either by the referring physician, by a medical consultant, or by the author. If any patient showed any physical ailment, either during the physical examination or in the laboratory tests, he was eliminated from the present study. All patients with neurologic disorders, although complicated by tension symptoms, were also excluded. Patients who were overtly psychotic were treated in the hospital, although some patients are included here who were felt to be on the borderline between anxiety neurosis and a psychosis. If the depressed patient did not respond to meprobamate in one week, he was removed from the study and was treated in some other manner. However, any patient who received the drug as part of his treatment was tabulated. The number of cases treated between the above dates was 200.

Dosage. Treatment was instituted in 14 cases during January, 1953, in doses of 500 mg. After a period of time, the tablet strength was reduced to 400 mg. for the remainder of the study.

Therapy was without difficulty or patient resistance. One 400 mg. tablet after each meal and at bedtime was the usual dose. Body weight made little difference, although some unusually large men needed an extra tablet or two.

During the present studies the largest amount of drug consumed by a single patient, over a period of more than 15 months, was 860 Gm. The maximum daily dose was eight tablets for a 105 pound patient with a tension state. This was reduced in 21 days to five tablets, and, after another week, the usual dose of four tablets daily was all that was necessary. This patient was weaned from the drug with no symptoms and classified as recovered in seven months.

Most patients were well adjusted to a standard dose of meprobamate, one tablet (400 mg.) after each meal and one at bedtime. There was a tendency to resist discontinuance of the bedtime dose, particularly if the patient remembered his insomnia of the time previous to treatment. A patient who has more than the usual resistance to sleeping will need a double bedtime dose.

Placebos. No separate group of control patients was used. During the course of the study, however, 16 patients taking the drug were transferred to placebos for control observations. All complained so much about the return of their symptoms before the end of the week that they had to be returned to meprobamate therapy.

Other Medication. Very few patients were given any other medication simultaneously with meprobamate. Alcoholic patients received bis (diethylthiocarbamyl) disulfide and sometimes insulin. (Details of treatment are given in the section "Clinical Findings.") Three patients having brain dysrhythmia or overt convulsions received diphenylhydantoin sodium or paramethadione. One Parkinson patient with organic confusion also received trihexyphenidyl hydrochloride. In 12 cases with mildly depressed symptoms, meprobamate was supplemented with 5 to 15 Gm. of dextrorotary amphetamine, or with amphetamine sulfate and the alseroxylon fraction of *Rauwolfia serpentina.* In combination, the drugs were usually able to lift the patient's mood and stabilize it toward the cheerful side. There were 10 successes and 2 failures in this group.

Electroshock Treatment. Patients with frank depressive psychoses were not put on drug

therapy but underwent electroshock treatment. Thirteen of these were treated with meprobamate for post-shock confusion to allay their tension and anxiety, and 21 cases received it to induce sleep during the week immediately following the termination of treatment. Fourteen patients who were not psychotic but who did have serious depressive symptoms did not respond to drug therapy treatment and were given electroshock treatment with uniform success.

Duration of Treatment. Patients were treated for periods of time ranging from less than a month to more than eight months. About one third of these, as can be seen from table I, were considered as fully recovered in this time, since they no longer had symptoms and no longer had to take a tranquilizer. In addition, one fourth of those labeled as improved were symptom-free but were still taking normal doses of meprobamate at the time of writing. Twelve cases remained chronic after eight months of treatment, although the drug dosage had been cut to one tablet a day.

Withdrawal of Meprobamate Therapy. Meprobamate was not found habit-forming in the pharmacologic sense, and tolerance did not develop. Long-time users did not require increased doses to get the tranquilizing effect but were able to cut down the dosage as desired. Sixty-three per cent of the patients discontinued taking the drug without difficulty and usually of their own volition. When the patient reported that he felt "as good as he ever did," the medication could usually be discontinued within a week. The remaining cases required more careful and gradual withdrawal. Various methods of withdrawal were tried.

The most effective method is as follows: After three months, when the patient feels well "most of the time," the noon dose is eliminated. After two weeks, the after-dinner dose is discontinued. The final step is taken in about three weeks.

This can be accomplished in either one of two ways. First by discontinuance of the morning dose and then of the bedtime dose. Second, by cutting the tablets in half and prescribing one half in the morning and the other half at bedtime. The tablet-splitting method, however, has the psychologic weakness of making the patient aware of how much he is being cut down, while the tendency to skip doses, on the other hand, is almost automatic.

Most of the patients who feel reasonably well can often skip doses at random until they find that they have run out of meprobamate and no longer need it. If the drug was withdrawn too quickly, a relapse resulted and sometimes required that the patient be restored to full doses for a short time.

CLINICAL FINDINGS AND DISCUSSION

Results by Diagnostic Classification. Table I shows the results of meprobamate treatment of 187 patients, classified according to diagnosis. Thirteen undiagnosed patients were not included in the tabulation.

The following remarks will clarify some of the terms used in the table: The behavior problem children were all restless and tense. Meprobamate was given to them primarily in the hope of helping them to quiet down, to concentrate better, and to be less disruptive in school.

TABLE I

The Diagnoses and Results of Miltown Treatment in 187 Psychiatric Patients

Diagnosis	No. of patients	Recovered*	Improved†	Not improved	% recovered or improved‡
Tension state	43	17	24	2	95
Anxiety state	29	10	17	2	90
Conversion hysteria	19	6	6	7	60
Alcoholism	10	5	4	1	
Behavior problems (children)	10	1	6	3	
Involutional depression	16	6	7	3	
Situational depression	7	3	2	2	
Manic-depressive psychosis					
(depressed)	6	0	3	3	
(manic)	4	2	2	0	
Postelectroshock confusion	13	9	3	1	
Organic confusion	9	2	5	2	
Psychasthenia	4	0	3	1	
Psychotic personality	5	0	1	4	
Paranoid state	4	2	2	0	
Schizophrenia	5	0	1	4	
Other diagnoses	3	1	2	0	
Total	187	64	88	35	80

* Patients were relieved of symptoms and able to make satisfactory social and work adjustments. Patients in this group had been completely withdrawn from meprobamate and had retained their improvement for at least six months.

† Patients were relieved of symptoms in varying degree, with better social and work adjustment. Improvement ranged from a moderate change to recovery, but in the latter case continuation of the drug was necessary, or withdrawal lasted for less than six months.

‡ The percentage was calculated only where the number of patients in a category was sufficient.

Most cases of involutional depression listed here were primarily depressed rather than tense and had a great deal of difficulty in standing the heat. They usually presented symptoms of fatigue and irritability after or during menopause, particularly after an artificial menopause. They felt inadequate but did not show feelings of guilt or remorse. The more serious cases, of course, were hospitalized and given appropriate treatment.

The term "psychasthenia" is used to refer particularly to the obsessive-compulsive-ruminative type of psychoneurotic who complained primarily of ideas that kept forcing themselves back into their consciousness or of actions they had to perform in order to remain comfortable.

The paranoid states listed were not overtly psychotic and had fairly intact personalities with some mild delusions, usually of infidelity.

The tension state cases were those who complained primarily of feeling "tight." They frequently said, "I get so tight and my muscles are so taut that I can't sleep" or "I feel like crying." Very frequently they had a headache that they localized at the base of the skull. These cases showed a minimum of fear and anxiety.

The anxiety state group were those who had very obvious symptoms of anxiety neurosis,[7] a generalized sense of dread that was not connected to any object, preoccupation with their symptoms so that it interfered with their daily work, marked irritability, sometimes loss of appetite, and evidence of glandular activity such as dilated pupils, rapid pulse, cold extremities, or complaints of unnecessary heat.

Alcoholism in the 10 cases used here applied to individuals who came to the psychiatrist while they were drinking and who were continued on meprobamate treatment. The few alcoholics who were hospitalized for withdrawal only, and took meprobamate for only a day or two, are not tabulated here.

The clinical data indicated that meprobamate was of considerable value in anxiety, tension states, and alcoholism. Conversion hysteria and behavior problems were also favorably influenced.

In alcoholism, meprobamate helped to avoid serious withdrawal symptoms and assisted in keeping alcoholics abstinent after withdrawal was completed. One procedure used was the initiation of treatment with large doses of insulin designed in part to give the patient an appetite and the reassurance that he could eat a good meal again. As soon as he could take medication by mouth, one tablet (400 mg.) every four hours was prescribed and continued until he was free of any complaints of tension, stomach distress, or headache. This took from 24 to 36 hours. Usually on the third day, after the Drunkometer showed the breath to be free of alcohol, therapy with bis (diethylthiocarbamyl) disulfide was instituted as follows: three tablets the first day, two tablets the second, and one tablet a day thereafter. The "test dose" of alcohol was not used. However, a strongly evil picture of the probable results if the patient backslides was drawn. The dosage was continued unchanged, one tablet four times a day thereafter.

In most instances, these alcoholics, particularly those who wanted to stay abstinent, said the treatment was of value to them and that they had not been taken off alcohol as easily before.

Results by Symptomatology. Table II shows results achieved according to major presenting symptoms. Discussion is limited to symptoms of highest incidence, namely tension, insomnia, depression, and headache.

TENSION. All but 7 of the 86 cases of tension showed marked improvement. Twenty improved rapidly enough to be discharged in a month or less. Most others were relieved after three to four months of treatment. Least responsive were those who had suffered from their psychiatric condition for more than 10 months prior to coming for treatment.

INSOMNIA. It was apparent from the start of this study that poor sleeping behavior was easily corrected. Since receiving meprobamate for clinical trial in January, 1953, barbiturates or similar somnifacients to engender sleep have not been required by any patient. By adjusting the dose of the drug, it has been possible to produce sleep in every case except

TABLE II

200 Cases Treated with Miltown
Results by Major Symptoms

Symptoms	Total incidence	Number improved	Per cent improved*
Insomnia	70	67	95
Tension	86	79	90
Headache (tension)	27	23	85
Anxiety and fear	21	18	85
Depressive symptoms	44	28	60
Obsessions	13	12	
Guilt feelings	11	11	
Menstrual stress	5	5	
Manic symptoms	4	3	
Miscellaneous psychosomatic symptoms	25	17	65
Total	306†	263	85

* Calculated only where total incidence was sufficient.
† A number of cases are listed more than once because of a combination of symptoms.

in those suffering from true psychotic depression. In these cases, sodium amytal, nembutal, carbrital, phenobarbital, and morphine also failed to produce sleep, and all finally had to be treated with electroshock.

Twenty-one cases who were recovering from electroshock treatment had considerable difficulty in going to sleep without medication for a period of from two to four weeks. In each of these cases a single tablet helped to bring on sleep, and the nightmares that so often occur upon discontinuance of electroshock treatments were not usually noted. Dreams almost never occurred with meprobamate. When the new tranquilizer was used to replace other soporifics, when dreams were the source of complaint, the dream disappeared. An interesting feature of sleep therapy under this drug is the lack of drowsiness during the morning when the medication has been administered the previous night, and the absence of a hangover or "dopey feeling" that is one of the most unpleasant characteristics of the older somnifacient drugs.

Depressive Symptoms. As mentioned in the section on procedure, patients suffering from true psychotic depressions were not included in this study. The cases enumerated in table II, therefore, include only neurotic symptoms, although some were severe and on the borderline of psychosis. Twelve patients with mild depressions who received amphetamine in combination with meprobamate are included in the table; 10 were improved. Patients who coupled the complaint of depression with vague fears and feelings of tension and anxiety usually derived benefit from the new drug. The more seriously depressed did not. Fourteen cases had to have electroshock treatments after the tranquilizer had been tried with unsatisfactory results.

Tension Headache. The most dramatic reports of recovery or improvement in the patients who were given meprobamate came from those patients whose chief complaint was tension headache. The tension headaches are usually located at the base of the skull and, except for 2 cases, were linked with a feeling of tension or a feeling of being "keyed up." A total of 23 of 27 patients with this complaint either recovered or reported sufficient improvement so that they were not concerned with this symptom.

Toxicity and Side Effects. Side reactions from meprobamate administration are minimal. Five patients complained of gastric discomfort after taking the drug when stomach pain or "gas" had not been complaints prior to its administration. On the other hand, cases quite frequently were seen whose original prime complaint was abdominal pain, disturbing motility, or eructation and, as can be seen in table I, a large number of these cases cleared up completely with the administration of meprobamate. Occasional patients complained of headache the first day or two of administration. These usually responded to a cup of black coffee.

A sensation of slight vertigo sometimes described by the patient as "I feel as though I had had a drink," indicates a need for reduction of the dosage. This is best accomplished by discontinuing the dose usually taken prior to the time of day when the patient feels abnormal.

Allergic Reactions. Only 3 patients were truly allergic to the drug. The first had two fainting spells and a temperature of 102 F. two and a half hours after two tablets. He was

given 150 mg. of tripelennamine hydrochloride orally every four hours, but it took two days to bring his temperature down and for the edema to disappear. He was not given further meprobamate. The second case developed urticaria after four days of drug treatment. She was given 50 mg. of diphenhydramine hydrochloride with each tablet, which controlled the urticaria. The third case developed an angioneurotic edema after six days. The edema cleared up in one day after discontinuance of drug therapy.

Overdosage. One great problem in the administration of the somnifacient and hypnotic drugs like the barbiturates, chloral hydrate, and their ilk has been the danger in ordering any large amount for a patient who might be on the verge of a depression and who, therefore, might take the whole prescription at one time with the intent of ending his life. In many instances individual doses had to be doled out by relatives, nurse, or others, and considerable watching was necessary. Every physician has seen cases where the patient was living alone and there was no one to see that he did not store up a few pills from each prescription until he had a lethal amount of sedative.

Because of the large number of patients and the long duration of the treatment, there were opportunities to see what would happen if meprobamate were taken in large doses. One patient took 50 tablets (20 Gm.) within 24 hours. Another also took a large amount, probably about 100 tablets, which he had hoarded. Both patients became deeply somnolent and experienced a drop of pulse rate. Both were readily roused with hot black coffee and being walked about. Both then slept for 10 to 12 hours and awoke without aftereffects.

These experiences indicate that a two weeks' or even a month's supply of the drug can be given the average patient who is living alone without danger of success if he uses it to try to take his life. Naturally, no one would be so unwise as to leave any powerful medication in the hands of a patient who is potentially suicidal.

Miltown and Psychotherapy. The therapist, at times, has cases with which he cannot become *en rapport.* Although meprobamate in the present series of cases was prescribed primarily to alleviate the patient's suffering, it was found that all patients became more responsive to suggestion, hypnosis, and free association (conversational or discursive) therapy. Several cases who had emotional blocking in early psychotherapeutic sessions responded adequately after taking the tranquilizer.

The feeling of ease and relaxation that meprobamate brought about definitely increased the patient's confidence in the physician and broke down his emotional defenses.

SUMMARY

Miltown is a practical, safe, clinically useful, nonaddictive tranquilizer. The syndrome in which it is of most value is the so-called anxiety neurosis, especially when the primary symptom is tension. The drug is also useful in helping alcoholics remain abstinent, after withdrawal is completed. Meprobamate appears to have some value in neurogenic conditions of the skin, in abdominal discomfort, and in several kinds of headache, particularly when associated with a psychologic factor. It also controls hypomanic syndromes sufficiently so that the patients can be tolerated in the community. Miltown is an effective

dormifacient and appears to have many advantages over the conventional sedatives, except in psychotic cases. It relaxes the patient for natural sleep rather than forcing sleep.

RESUMEN

Meprobamato (Miltown) es un agente tranquilizante de utilidad clínica, práctico y seguro que no causa habituación. El síndrome en el que es de más valor es en la llamada neurosis de ansiedad, especialmente cuando el síntoma primario es la tensión emocional. Este agente es también útil para mantener en estado de abstinencia a los alcohólicos durante las curas de desintoxicación. Parece también tener cierto valor en los procesos neurogénicos de la piel, molestias abdominales y en diferentes tipos de cefaleas, particularmente cuando tienen un componente psicológico. También domina los síndromes hipomaníacos lo suficiente para que los pacientes puedan ser tolerados en comunidad. Meprobamato es un hipnótico eficaz que parece tener muchas ventajas sobre los otros tipos de sedantes, excepto en los casos psicóticos. Produce un relajamiento en el paciente que induce a un sueño natural.

RESUME

Meprobamate (Miltown) est un calmant pratique, anodin, d'utilité clinique et non habituant. Sa plus grande valeur se montre dans le syndrome de la soi-disante névrose d'anxiété, particulièrement quand le symptome primaire est la tension. Cette drogue sert aussi à aider les alcooliques à maintenir l'abstinence une fois la suppression de l'alcool est accomplie. Le meprobamate semble être d'une certaine valeur dans les conditions névrogeniques de la peau, dans le malaise abdominal et dans plusieurs formes de maux de tête, particulièrement ceux qui sont liés à des facteurs psychologiques. Il impose assez de contrôle aux syndromes hypomaniaques pour rendre les affligés tolérables à la communauté. Meprobamate est un somnifère efficace et, sauf dans les cas de psychose, semble posséder beaucoup d'avantages sur les sédatifs conventionnels. Il dispose le malade à s'endormir naturellement, au lieu de forcer le sommeil.

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INTERNATIONAL SYMPOSIUM ON CHLORPROMAZINE

PART I*

The Challenge of Bio- and Chemotherapy in Psychiatry

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I

"The purpose of Chemistry," said Paracelsus, "is not to produce gold, but to study the basic sciences and use them against disease."

The new narcobiotic, chlorpromazine, represents a crystallization of Paracelsus' dream, which has come true as modern medicine keeps adding synthetically produced drugs to the psychiatric arsenal.

For almost 2000 years the physician has been steadily progressing in the field of clinical diagnosis and enlarging his etiologic knowledge of disease. But therapy has been the slowest wheel on the wagon of medical progress. Perhaps as a result of the galenic concept of the treatment of disease, which often confused symptoms with causes, at the end of the last century therapy was in some respects as symptomatic and empirical as it was in the days of the school of Salerno, for it drew heavily from herbs and plants.

Our century has provided medicine with a springboard of new biologic, endocrinologic, and antibiotic therapies. The researcher has thrown himself into laboratory work to discover chemical substances endowed with therapeutic powers—Paracelsus' ancient dream was finally fulfilled in Ehrlich's laboratory.

Ever since the first salicylates were synthesized in the last century, medicine has steadily grown richer in chemotherapeutic substances. As the physician has learned to aim his weapons at the etiologic cause of disease, the quest for specific chemotherapeutic agents has become keener.

For the last 10 years the pharmacologic laboratory and the pharmaceutical industry have inverted the historical order in the quest for therapeutic agents.

In the beginning of the bio-chemotherapeutic era most drugs were born out of the practicing physician's need for a concrete answer to abstract problems of disease. Today drugs are born of the slow, methodical quest carried out by the chemist for compounds that are then cast by the clinician into the living crucible of a hospital to determine their range of action.

* Part II of this symposium will appear in the April-June issue.

No longer do drugs arise directly from the pressing needs and daily frustrations imposed by medical practice on the physician, who in the past had little with which to treat his patient. Today they arise from the ceaseless search of the laboratory investigator for chemical substances whose clinical usefulness can only be determined by the physician at the patient's bedside.

II

Chlorpromazine—one of the greatest pharmacologic aids to modern psychiatry—is the result of research at the Rhône-Poulenc Laboratories (Paris) into the pharmacologic properties of phenothiazine derivatives, which were considered effective against trypanosomiasis and malaria.

One of these derivatives, promethazine, was shown to possess low toxicity and antihistaminic properties, and it, therefore, was used at first in the treatment of allergies. However, it was discovered that one of its secondary effects was sedative and hypnotic; Moindrot showed this to be true in 58 per cent of all cases, while Halpern and Briot demonstrated that its action was located in the diencephalon. These facts led to the search for further derivatives. Diethazine, isothiazine, and thiazinamium (3554 R.P.), with their notable anticholinergic properties, were isolated. The tireless search then continued.

In December 1950, Charpentier (Research Department of Rhône-Poulenc) synthesized 10-(3′-dimethylaminopropyl)-2-chlorophenothiazine, whose pharmacodynamics were studied under the laboratory number 4560 R. P. by Courvoisier, Kolsky, Fournel, Ducrot, and Koetschet. This preparation was introduced to the medical profession in Europe in November 1952 as Largactil.

Chlorpromazine, as it came to be called, was found to exercise its effects on the central and peripheral nervous systems and was also established as having a thermoplegic, anticonvulsive, ganglioplegic, and sympathicoplegic action. This drug was later described as a narcobiotic by some and as a neuroleptic or an ataractic by others.

The semantics of these drugs are truly fascinating. As Decourt has stressed, we must differentiate between the *pharmacodynamic action* of a drug as shown in the laboratory and its *therapeutic* technique—the use, alone or in combination, of pharmacodynamic resources having a common therapeutic goal.

We must also differentiate among *neuroplegia* (deep, controlled, and temporary inhibition of the neurovegetative and central nervous systems in order to provoke a healthy hypometabolism), *artificial hibernation* (neuroplegia plus refrigeration), *potentiated anesthesia* (total effect of two or more combined medications that is greater than that obtained by merely doubling or multiplying their dosage), and *narcobiotic action* (a drug-induced inhibition of certain basic metabolic activities of the living cell, total or partial, reversible or irreversible).

Chlorpromazine was the result of 20 years of research directed toward the discovery of a drug that would prevent or correct the effects of the phenomena of Reilly—the hemorrhage, vascular and lymphatic lesions of the alimentary tract, and necrosis of the adrenal glands that occur subsequent to the irritation of the sympathetic nerves.

The trial of antihistaminic drugs led to the isolation of phenothiazine derivatives; prome-

thazine proved to be a "potentiator" of certain anesthetics (Laborit, 1950). Chlorpromazine protected 70 per cent of guinea pigs (Reilly et al, 1953) against splanchnic irritation and prevented the response of the pituitary-adrenal axis to nonspecific aggression through its central depressant action on the reticular formations of the brain.

Laborit and Huguenard used chlorpromazine as part of their "lytic cocktail" (in combination with Phenergan and Dolosal) to block the neurovegetative nervous system to induce "artificial hibernation." Thus, they sought to combat shock, facilitate surgery, potentiate anesthesia, and intensify the effect of barbiturates and narcotics. This was of immense importance in treating patients with inoperable cancers who were condemned to a life sentence of narcotics to relieve the tyranny of pain.

Artificial hibernation, and its modification as prolonged narcosis, had been under fairly intensive investigation abroad, especially since Klaesi's basic psychiatric work in the second decade of this century. However, while many investigators—among them the eminent clinician and psychoanalyst Johan H. W. van Ophuijsen—were encouraged by the therapeutic benefit afforded by this procedure, the mortality rate led to a reaction against its use. The revival of interest in this approach came during the first years of the current decade—with the advent of antibiotics—and more recently, when Henri Laborit (France) reported the marked effects of chlorpromazine on the autonomic nervous system, including the temperature-regulating mechanism.

The use of chlorpromazine in psychiatric disorders soon followed. It was first reported in France by Hamon; Paraire and Velluz; Deschamps; and Delay, Deniker, and Harl. In the report of the last group (Delay et al), the relationship to artificial hibernation as well as its sympathicolytic central action was noted.

Following upon research work overseas, Lehmann and Hanrahan (February, 1954) and Winkelman (May, 1954) introduced this new pharmacodynamic agent in Canada and the United States, respectively.

The clinical spectrum of chlorpromazine increases every day and reports relate to its use in acute and chronic alcoholism, manic-depressive psychoses, control of agitation in schizophrenic patients, symptomatic control of confusions of a toxic origin, alleviation of tension in psychoneurotics, acute toxic delirium, and epileptic confusion.

The most promising field for chlorpromazine appears to be psychiatry. It is postulated that by depressing the autonomous nervous system and interfering with the synaptic transference of excessive psychomotive excitation between the cortical areas and the diencephalon, chlorpromazine tranquilizes without producing narcosis, coma, or amnesia. Inhibition of anxiety increases the patient's capacity to respond to psychotherapy.

From the vast range of clinical investigations under way today, it seems that chlorpromazine helps control hyperactivity and anxiety as well as improving communication with the patient, thus permitting the utilization of psychotherapy.

It is our hope that further investigation of the mechanism of action of this and other pharmacodynamic agents, together with continuing studies of the earlier physiodynamic therapies (insulin, thyroid histamine, testosterone, and electroconvulsive therapies), will bring to light new clues to aid the search for etiologic and pathogenetic mechanisms at the

root of the most distressing psychiatric disorders. The so-called "functional psychoses" will be seen more clearly as psychoses due to dysfunction, and the basis of the dysfunction will be more readily comprehended. And, with increased insight into etiology and pathogenesis, added to the present store of knowledge of symptomatology (Kraepelin-Bleuler) and psychodynamic symptom formation (Freud), we believe the development and growth of a mature scientific psychiatry is heralded. With this, the fundamental fusion of psychology and biology—the most comprehensive concept of psychobiology—will be exposed to analysis and synthesis.

If we hold the sixteenth century to be the century of anatomy, the seventeenth that of the birth of modern physiology, the eighteenth that of medical philosophy, and the nineteenth that of histopathology and clinical etiology, the twentieth century is the century of biochemotherapy—the new key to the future of psychiatry as well as medicine.

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Chlorpromazine and Neuroleptic Treatments in Psychiatry

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It is now four years since chlorpromazine was introduced into psychiatric therapy, and in that time it has risen to the first rank in biologic treatments employed in specialized services. If 1952 was the year of its discovery, and 1953 and 1954 the period of extending the use of the new treatment, one can say that 1955 was the year of comparison of results; in effect, that year was marked by a number of national and international conferences devoted to those new forms of medication that we propose to call "neuroleptic."

In April in Barcelona,[1] in June at Philadelphia,[2] and in the fall in Italy,[3, 4] meetings were held that preceded the International Conference that we were honored to organize in Paris.[5] At this meeting, attended by more than 400 psychiatrists, 22 nations were represented by eminent clinicians, of whom several have also collaborated in this special issue on chlorpromazine in psychiatric therapy. The focus that this issue brings to the discussion thus seems to us to be remarkably opportune.

It is, nevertheless, difficult to present in a few pages a general view of the questions that should be raised. At the present time the publications devoted to chlorpromazine and similar drugs are, so to speak, innumerable; the International Conference in Paris, which recently focused discussion, alone included more than 150 papers. We will, therefore, confine ourselves to an attempt to sketch the main lines of the most important chapters.

HISTORY

It would be possible to show the relationship between the new therapy and the various methods and medications used earlier as sedatives for the central and vegetative nervous systems. One could also claim that a medical discovery proceeds essentially from an idea and from a fact: the idea is that which guided those who sought means of blocking the essentially nervous mechanism of shock reactions, of alarm, and of irritation; the fact was the appearance of a chemotherapy that permitted an effective action on this mechanism.

The introduction of chlorpromazine into psychiatric therapy stemmed from the work of Laborit on artificial hibernation, but the use of this medication in our discipline is done most frequently, not by the Laborit method, but by the technique of administering the medication alone in prolonged treatments that we propose to call "neuroleptic" treatment. In this regard, we recall that our first publication was done on the occasion of the centenary of the Société Médico-Psychologique in May, 1952, which was devoted to "Shock and Alarm Reaction." In opposition to the methods of shock and stimulation, we presented the

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inverse method of calming the nervous system and of sedating the irritative, biologic, and psychologic processes.

ADMINISTRATION AND DOSAGE

We have noted that chlorpromazine can be used in artificial hibernation, in which the psychiatric indications are limited to severe or hypersevere syndromes. Chlorpromazine can also be used to induce sleep therapy, continuous or not, for which we believe that the indications are equally limited.[6]

In effect, the method of using chlorpromazine alone is the one that has been widely used in psychiatry in the treatment of psychotic, neurotic, and psychosomatic states. The association of shock treatment with neuroleptic treatment has been shown to be possible; similarly, in certain cases chlorpromazine aids psychotherapy and occupational therapy.

Some interesting therapeutic trials have been effected with the association of mescaline and chlorpromazine.[7]

As regards dosage, we have in a large number of cases remained faithful to daily doses of the order of 150 to 200 mg. However, Staehelin and his collaborators (Basel) introduced higher dosages, particularly in the treatment of schizophrenia; as regards schizophrenics, we have confirmed the merits of Staehelin's viewpoint, although we rarely exceed doses of 250 to 500 mg. daily, even in the treatment of chronic psychoses.

Very high dosages, reaching several grams daily, have also been recommended, but it does not seem to have been demonstrated that these exercised any better effects, although more rapid ones. Some workers systematically look for the appearance of extrapyramidal symptoms as evidence of the drug's effect. Very low dosages have also been advocated (a few tens of milligrams daily by Baruk), and it sometimes happens that these are effective.

The conclusion reached at the recent Paris Conference in the matter of dosage could be expressed thus: there is no standard dosage; on the contrary, chlorpromazine must be administered according to the variable individual susceptibility toward this product.

PRINCIPAL INDICATIONS

It is not possible to give details of all the psychiatric indications for treatment with chlorpromazine, dealt with in an abundant literature to which we have contributed a certain number of publications. We will, therefore, limit ourselves to underlining certain points that appear to us to be essential ones.

In the field of psychoses, we are first concerned with the manic-depressive state; it should be emphasized that there is a difference in the results obtained, depending on whether one is dealing with the manic or the melancholic phase. In the first case, our data covering nearly four years allow us to note a success rate of more than 85 per cent, with a clear reduction in the duration of the attack, in comparison with earlier treatments; contrariwise, if chlorpromazine can be useful in the treatment of certain depressive states, it only rarely cures real melancholia for which one still has to have recourse to electroshock treatment, with which chlorpromazine can be gainfully associated.

We are secondly concerned with the possibility of treatment of chronic psychoses with chlorpromazine. The indications for this medication in the acute and subacute stages are well known: the syndromes of excitation, agitation, anxious or aggressive tension; the states of mental confusion; the attacks of delirium; and in general all cases of a certain severity can be improved or cured, even if they appear in the course of a chronic psychosis. In the light of the most recent work, it appears possible to agree that prolonged treatment with chlorpromazine can profoundly modify chronic psychoses. In reviewing the case histories of more than 300 patients, hospitalized and treated with chlorpromazine since 1952,[8] we have noted that this is indeed the case.

In the field of schizophrenia, the paranoic forms appeared to us to be more clearly benefited than the hebephrenic or hebephrenocatatonic forms. Nevertheless, statistical data show that the chances of improvement with chlorpromazine regularly decrease in proportion with the duration of the psychosis.

The action of the drug on paranoic schizophrenics can be compared with the effects we have noted in chronic delirium states, whether hallucinatory, interpretative, or passionate. Although in such cases it is difficult to claim a complete cure, it is at least possible to produce a patient's gradual disinterest in his delirium, which will lead to his discharge from the psychiatric hospital and his social convalescence. This effect of disinterestedness is for us the principal psychologic action of the drug.

In the field of neuroses, it is relatively more difficult to codify the indications, although the use of this drug is more extensive there. We originally emphasized the good symptomatic effects of the medication in cases of neurotic tension, anxiety, and for facilitating sleep; on the other hand, the product appeared to us to be contraindicated in conditions dominated by asthenia, which it actually aggravates.

In our knowledge there are no important data on the drug's therapeutic results in the field of the neuroses that would allow a nosographic precision of its indications. We will shortly publish our data since 1952, which will follow those on the psychoses. Actually, the most interesting work is that which permits an objective comparison of the effects of chlorpromazine with those of the classic sedatives; the work of Linford Rees,[9] for example, establishes the indisputable efficacity of phenothiazine.

ACCIDENTS AND CONTRAINDICATIONS

Although rare, the accidents with this remarkable drug are not to be neglected. We are not concerned here with the orthostatic disorders found at the start of treatment, nor with the painful indurations due to repeated injections, both of which are mere incidents.

The cutaneous intolerance, rare among patients, is much more troublesome to the nursing personnel who are regularly called upon to manipulate the drug. Almost exclusively confined to the female personnel, these disorders consist of erythemas that are generally sensitive to sunlight, and of acute or subacute eczemas that in many cases prevent subjects from having any contact with the medication. These constitute a veritable professional hazard that can raise medicolegal questions.

The jaundice associated with chlorpromazine, whose mechanism is still obscure, appears with variable frequency according to countries. Our data show no more than 4 per 1000, although it should be noted that we do not exceed dosages of 500 mg. per day. As for extrapyramidal symptoms, we will deal with them in a separate paragraph later. While some consider them as a complication, others see in them evidence of the drug's activity.

Phlebitis, with possible pulmonary or cardiac infarction, is rare, although it constitutes the only really serious complication of the drug that might give rise to contraindication.

We should also note rheumatoid arthritis, galactorrhea, and, in the psychic field, the possiblity of depressive phases in the course of treatment.

During the International Conference in Paris, it was justly emphasized that individual susceptibility played a major role in the genesis of complications, the frequency of which was not proportionate to the size of dosages used.[10] We also believe that individual reaction is of great importance in neuroleptic treatment, and that dosages must be adapted to each case. As regards complications, individual susceptibility appears to us to be undeniable, even though such complications have been rare with the dosage recommended by us. The incidence of jaundice in our data is lower in comparison with the data of Swiss and American authors; as for the extrapyramidal symptoms, we observed these only when the dosage exceeded 250 mg. per day.

CHLORPROMAZINE AND RESERPINE

In the last two years, reserpine, the alkaloid of *Rauwolfia serpentina*, was introduced into psychiatric therapy, and its action has been compared to that of chlorpromazine.

Differing greatly in its chemistry, reserpine has an action that is slower, more irregular, less constant, and generally less powerful than chlorpromazine; some of its vegetative effects are either opposite or different. Nevertheless, these two drugs have in common certain special effects that distinguish them from previously known drugs. The most remarkable effect from the psychiatric standpoint is the sedation and the inducement of sleep without narcosis, at whatever dosage is used. These two drugs also share the curious property of being able to produce extrapyramidal symptoms that are always reversible on cessation of treatment. In their regard, can one speak of a parkinsonian syndrome? Tremors are noticeably more rapid (nine per second), and one must emphasize the frequency of acathexia and impatience in these syndromes that can, in other ways, comprise authentic parkinsonian signs varying from patient to patient.

The similarity of the special effects produced on the nervous system by both substances encouraged us to consider them as a new group of compounds distinguished more by their effects than by their chemical composition, to which we proposed to give the name of neuroleptics, a term that was approved by the participants in the International Conference in Paris. It is likely that in the future new neuroleptic drugs will enrich this group.

MODE OF ACTION

While the mechanism of action of reserpine, according to pharmacologists, appears to be

essentially on the central and subcortical nervous system, the action of chlorpromazine appears to be infinitely more complex.

The inhibitory action of this compound on the reticular substance of the brain stem, demonstrated by Dell and co-workers, is not in question, but it cannot be simply explained as an effect on the function of sleep. We insisted from the start on the fact that the initial somnolence produced by the drug was transitory, and that the most characteristic psychic effect lies in the state of disinterest and psychoaffective calm that results from treatment; one could, on the other hand, admit that the state of psychic disinterest is a preparatory stage of sleep.

The neurophysiologic changes produced at the level of the reticular substance undoubtedly find an echo in those areas of the brain that are connected with this center, notably in the cortex. Further, some authors have insisted on the possibility of a pituitary-hypothalamic action. The remarkable action of this drug on mental syndromes that are generally recognized as having a pathogenic origin in the subcortical region is a strong argument.

Furthermore, the peripheral action of the drug, notably on the sympathetic vascular system, is not negligible, as Dell showed when demonstrating its action on the reticular substance. The explanation of the complex mechanism of action of chlorpromazine has even gone as far as Laborit's recent suggestion that there may be involved a cellular action comprising a change in the bioelectric charge of cellular potassium ions.

CONCLUSION

The meeting in Paris of most of the workers who have studied the use of chlorpromazine in neuropsychiatry, and the exchange of their opinions, made it possible to reach the following conclusions: The efficacity of treatment with chlorpromazine in psychiatry is certain, the drug actually being placed in the front rank of biologic therapeutic agents used in our discipline. The remarkable results obtained with this medication, however, should not reduce the importance of a preliminary diagnosis, of concomitant psychotherapy, and of eventual readaptation of the patient. The safety of treatment is only relative, though the incidents and accidents are generally considered as of secondary importance in the light of the benefits derived from the use of the medication in the treatment of mental disorders. It would appear that chlorpromazine is the first drug in a series, the use of which in prolonged and continuous treatment sets them apart as biologic therapeutic agents. The contrast is made between shock treatment and neuroleptic treatment.

RESUMEN

La reunión celebrada en París (Francia) por la mayoría de los investigadores que han estudiado el uso de la clorpromazina en neuropsiquiatría y el consiguiente intercambio de opiniones, hizo posible llegar a las conclusiones siguientes: La eficacia del tratamiento con clorpromazina en psiquiatría, es cierta; el medicamento en la actualidad se halla a la cabeza de los agentes biológico-terapéuticos utilizados en esta especialidad. Los notables resultados obtenidos con la clorpromazina no deben, sin embargo, reducir la importancia de un diag-

nóstico preliminar, de la psicoterapia concomitante y de la readaptación eventual del paciente. La innocuidad del tratamiento es sólo relativa, aunque los incidentes son considerados por lo general como de secundaria importancia a la luz de los beneficios derivados de su uso en el tratamiento de los trastornos mentales. La clorpromazina parece ser la primera en una serie de drogas cuyo uso en un tratamiento continuo y prolongado las coloca en un plano aparte como agentes terapéuticos de tipo biológico. En este trabajo se expone el contraste existente entre el tratamiento por el choque por los agentes neurolépticos.

RESUME

La réunion et les discussions à Paris de presque tous les chercheurs qui ont étudié l'emploi de la chlorpromazine dans la néuro-psychiâtrie, rend possible les conclusions suivantes: La chlorpromazine est d'une efficacité certaine dans le traitement psychiâtrique, en fait, elle se place au premier rang des agents biologiques de thérapie employés par notre discipline. Cependant, les résultats remarquables obtenus par cette médication ne doivent pas éclipser l'importance d'un diagnostic préliminaire, d'une psychothérapie concomittante, et d'une réadaptation eventuelle du malade. La sécurité du traitement n'est que relative, quoiqu'à la lumière du bien qui résulte de son emploi dans les désordres mentaux, les accidents et incidents qui se produisent n'assument qu'une importance secondaire. La chlorpromazine semble être la première dans une série de drogues dont l'emploi dans les traitements prolongés et continus, les met à part comme agents biologiques en thérapeutique. Le contraste est présenté entre le traitement par l'éléctro-shock et le traitement néuroleptique.

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Pharmacodynamic Basis for the Use of Chlorpromazine in Psychiatry

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In the first part of this review we will attempt to show how, with the aid of simple methods, it is possible to study in laboratory animals the various main properties of chlorpromazine at present usefully employed in psychiatry.

The first series of tests illustrates the onset of a state of psychic indifference in an animal treated with chlorpromazine: indifference to a stimulus conditioning a notion of pain (conditioned reflex test); indifference to pain itself (psychoanalgesic action); indifference to metabolic stimuli, such as hunger or thirst (maze test); and indifference to a trophic instinct (spider web test). The second series of tests measures the extent of the sedative action of chlorpromazine: action on spontaneous motility (Winter's mirror-cage test and Wahmann's drum test) and action on equilibration reflexes (Joulou's traction test and Baruk's experimental catatonia test). The third series determines the role of chlorpromazine in hallucinatory states (antihallucinogenic action in the mescaline syndrome).

The second part reviews the various experiments conducted to localize the point or points of impact of chlorpromazine action in the different zones of the central nervous system. The introduction into psychiatry of reserpine, which in this clinical field possesses properties similar to those of chlorpromazine, will no doubt considerably enrich our understanding, as yet very hypothetical, of the mode of action of these two products.

Although chlorpromazine now has an important place in modern psychiatric therapy, hallowed by a wealth of clinical experiments as widespread as they are varied, the mechanism of action of this compound in the central nervous system remains hypothetical. In effect, the numerous attempts to explain its action on the basis of data from neurophysiologic experiments in the laboratory show that today the problem is one of the most complex ones demanding solution. We have here attempted to give only a general review of the various researches, among which we included our own work, without attempting to present an exhaustive review of the question, a difficult task in view of the rapidity with which new reports are published.

In 1950, when the scientific services of the Rhône-Poulenc Specia Laboratories undertook research in the central activity of amines derived from phenothiazine, which eventually led to the discovery of chlorpromazine,[14] the neurotropism of these compounds, clinically reported some years previously by Sigwald,[63] had already been tested in animals by Winter and his co-workers. This researcher, using original techniques from which we subsequently drew inspiration, showed in 1948[73] that promethazine prolonged the duration of hexobarbital narcosis in mice and, in 1949,[74] simultaneously with Macht and Hoffmaster,[53] he showed

that antihistamine drugs could inhibit the activity of rats trained to climb a rope. The experiments of Winter and Flataker[75] on the performance of trained rats demonstrated that products such as promethazine inhibited instinctive and intelligent action in animals, apart from any apparent depressive action. The importance of this experiment encouraged us, at that time, to make a comparative study of the action of chlorpromazine on the cerebral activity of animals, inasmuch as this compound already showed laboratory promise in the field of anesthesiology.

As we required a technique in which the cerebral cortex of the experimental subject would play a preponderant role, excluding all secondary interference due to the individual's metabolism as is the case in the Winter experiment, we created a conditioned reflex in the rat by conforming as strictly as possible to Pavlov's rules,[43] his long classic work having represented an immense progress not only in physiology but also in psychology. In this type of reflex, direct excitation does not trigger the reflex itself, but it requires association with a precise and striking condition that is the additional stimulus required for success. A reflex of the same type was described by Sivadjian,[65] who trained rats to jump over a barrier, using the shock of an induction current produced by a Du Bois-Reymond trolley as the direct excitation and the noise produced by an oscillator at its highest frequency as the conditioning excitation. After a short training period, the rat jumped over the barrier at the mere sound of the oscillator, without any concomitant shock. The rat is an intelligent animal, particularly well suited to the type of study in which a conditioned reflex can be rapidly established. In our own tests, the auditory stimulus was provided by ringing a bell. The response was flight from pain, based on the rat's natural aptitude for climbing. The equipment consisted of a sound-proof cage in which a vertical rope was stretched between an electrified floor and a rest platform. The test consisted of two parts; counting the number of stimuli required to provoke the rat's reflex and clocking the climbing time. Bells were sounded every 5 seconds, lasting for 2 seconds. At the end of 30 seconds, a rat that had not completed the course was considered deconditioned. The normal rat completed the course in two to three seconds after one stimulus. We noted that, in thousands of animals, this type of conditioned reflex persists as long as the experimenter desires, providing it is kept up by two tests a week. In our own experiments, we determined that it persisted for at least a year.[15]

The first comparative studies we made, in July, 1955, on promethazine and chlorpromazine showed from the start that animals treated with the two products presented entirely different behaviors. At dosages varying from 1.0 to 5.0 mg./Kg. of body weight subcutaneous, promethazine exerted no modification on the conditioned reflex. At a higher dosage (10 mg./Kg. subcutaneous) the climbing speed becomes slower, without reducing the speed of response to the first stimulus. With chlorpromazine, however, one finds that low doses (1.0 mg./Kg. subcutaneous) definitely retards the response to the auditory stimulus, as well as slowing down the speed; and at increased doses, there is a total inhibition of the response. In general, the rat treated with chlorpromazine becomes disinterested in the bell ringing, which no longer incites flight from pain. As with an untrained normal rat, the subject moves curiously around the cage without paying attention to the auditory stimuli, or to

the vertical cord, although his interest can at any moment be awakened with some foreign excitation.

In a second series we used the same test to experiment with other drugs, such as phenobarbital, butobarbital and morphine, having a well known central action and classically used in preanesthesia medication. These showed no activity outside of their hypnotic action. Chlorpromazine, which potentiates narcosis, therefore possesses a specific activity not shared by either promethazine or the barbiturates.

Guha et al,[37] using an analogous type of acoustic conditioned reflex, confirmed our results with chlorpromazine. Archer[3] also studied the behavior of animals treated with chlorpromazine and used problems of varying difficulty, such as the maze test. This author trained rats stimulated by deprivation of liquid to circulate in a maze of 12 circumvolutions until they made no errors and found at the end the water they needed. He noted that chlorpromazine in low dosage (0.5 mg./Kg. subcutaneous) had little effect on the number of errors or on movement, although the rats lost some precision and speed. With higher doses (1 mg./Kg. subcutaneous) he noted a significantly lower speed without any great increase in the number of errors. Having completed the maze, however, the rats attached no importance to drinking; the absolute stimulus having lost its importance would explain their slower speed. Thus chlorpromazine provokes forgetfulness of motive before significantly modifying behavior.

In another type of test, fasting rats were trained in Omwake's maze[55] to find food at the end of the course. Guha and co-workers[37] found that a dose of 3 mg. was required to increase significantly the travel time. The work of Witt and Heimann[78] should be added to these experiments. They found that chlorpromazine completely suppressed the weaving instinct in the spider, clearly differentiating it from the hypnotics that leave this instinct more or less intact but interfere with the execution of the web.

We confirmed the indifference to sensorial stimuli created by chlorpromazine when we studied its possible analgesic action. Using the technique of thermoanalgesia described by Jacob,[41] we placed mice on a plate heated to 61 C. (141.8 F.). In seven seconds the mouse manifested signs of abnormal sensation by licking its front paws; in 15 to 20 seconds it showed disordered agitation and signs of growing anxiety. The violent vertical leaps that appeared in 30 to 40 seconds indicated the perception of insupportable pain. In the mouse treated with chlorpromazine, the first sensorial symptoms and the signs of disorder were suppressed. Only the vertical leap was brutally produced, precisely at 30 to 40 seconds, as in the controls, without any premonitory sign. In regard to this we note the observations of several authors that the mechanism of analgesia, in certain cases, makes patients more or less indifferent to pain without thereby delaying the percepton of the pain itself.[42–62] Fabris[31] states, in connection with the treatment of cancer pain with a combination of promethazine and chlorpromazine: ". . . during the first three or four days, from the first hour, one obtains a sensorial inhibition, psychic disinterest and, it seems, a state of well being that facilitates sleep." This author, however, was careful to dissociate the respective therapeutic action of each drug: ". . . the first of these two compounds possesses two properties important in cancer pain: it is both antihistaminic and hypnogenic; the second, called

neuroplegic, provokes a psychic inhibition, a psychosomatic rupture comparable to that which follows lobotomies."

The sedation effect of chlorpromazine was demonstrated in a series of simple tests on mice and rats that tested their motility and equilibration function.

Heim and Frodl[39] found that the spontaneous motility of mice was reduced from 20 to 100 per cent by the administration of 5 mg./Kg. subcutaneous of chlorpromazine. Boyd and Miller[9] obtained, with 2.5 mg./Kg. subcutaneous of chlorpromazine, a very important inhibition of locomotor activity of a rat placed in the Wahmann drum. Fournel,[34] using the Winter-Flataker mirror-cage,[76] found that a dose of 4 mg./Kg. administered orally was sufficient to reduce the spontaneous activity of the animal by 50 per cent. The traction test studied by Julou[45] consisted of suspending mice by their front paws from a metallic wire strung horizontally. Any animal that did not succeed within 5 seconds in bringing at least one hind paw up to the wire was considered to be under sedation; moreover, any animal in which there was not even a prehensile reflex was considered under hypnotic action. This test, which brings into play equilibration, muscle strength, and tonus, is of value in studying products with a depressive action.

Chlorpromazine, from the first dose of 5 mg./Kg. subcutaneous, rendered the mice incapable of traction (sedation), but the prehensile reflex subsisted as far as subtoxic doses. At 100 mg./Kg. subcutaneous, the mice remain suspended and inert in the position in which they were placed. The product is, therefore, a depressant at increasing doses without becoming definitely hypnotic, even at very high dosage.

Phenobarbital exercises sedative effects only at the dose of 30 mg./Kg. subcutaneous, but at a dose of 80 mg./Kg. subcutaneous it suppresses the prehensile reflex, which indicates the appearance of hypnotic action. Butobarbital rapidly becomes hypnotic (50 mg./Kg. subcutaneous) without any marked depressant phase. Promethazine produces neither sedation nor true hypnosis, but it does produce a state of torpor interrupted by more or less violent convulsive movements. It is practically impossible to study it in this test.

Another type of experiment confirmed these results. We registered the immobility created by chlorpromazine in mice with the aid of an electronic oscillograph that records imperceptible movements in animals. We found that chlorpromazine provoked in the mouse a state of peripheral muscular inertia similar to the state of natural akinesia of the frog described by De Jong and Baruk.[22]

Such immobility can not, on the contrary, be obtained with either butobarbital, hexobarbital, or promethazine, but only with phenobarbital at subtoxic doses. Baruk and his co-workers[4,5] showed that high doses of chlorpromazine produced in the mouse and the monkey an experimental catatonia as typical as that obtained with bulbocapnine. The symptomatology described by these authors is the same as that which we observed in our mice, treated with the same product, when they were suspended from the wire by one or two paws and maintained an active hold without falling off, all the equilibration reflexes being preserved. As described by Baruk, chlorpromazine allows one to follow, according to dosages, all the phases of an authentic catatonia which—and this speaks in favor of the low toxicity of the drug—does not appear until relatively high doses are administered.

The hallucinogenic properties of mescaline have been known for a long time and have been profitably used by certain psychiatrists (Salomon[60] and Fischer[33]). Workers generally admit that this drug disorganizes the subconscious in such a way that memories or suppressed events reappear with remarkable clarity and effect a transfer to a materialized infantile image.

However, Denber and Merlis[26] consider that the valuable therapeutic properties of this compound have not received enough attention so far, probably because of the unpleasant secondary effects that accompany its injection. Thus: ". . . following the injection of mescaline, one observes numerous conflicts expressed verbally and symbolically by the majority of subjects. There was hostility and aggression towards neighboring subjects, and one of the patients developed an acute destructive reaction that required the use of a straitjacket." These authors thought of investigating whether chlorpromazine could inhibit the effects of mescaline in man, and the favorable results they obtained encouraged us to verify them in animals.

In general, the study of hallucinatory states created by mescaline in the animal is not far advanced, although pharmacologic studies on the drug have been done for some time.[59, 60] De Nito[27] found that the administration of 20 to 30 mg. of mescaline increased the reflexes of the frog, and the hypodermic injection of 100 to 200 mg./Kg. intensified sensitivity to pain and agitation states in the guinea pig. Divry and Evrard[29] showed that mescaline blocked the development of catatonia due to bulbocapnine. Special mention should be made of the work of Sivadjian[65] who, with the aid of his conditioned reflex test, described, for the first time, the state of mescalinization in the rat: ". . . After an injection of 100 mg./Kg. one observes hallucinatory phenomena. Normally, when the animal hears the noise of the vibrator he changes compartments precipitatedly but without executing the sudden leaps that occur only when he feels a shock in his body. At that moment, the passage of the current causes it to utter a cry of pain. But with mescaline, if the noise is repeated without the accompaniment of the shock, the animal leaps up and down and utters cries exactly as if it had received the electric shock. One can suppose that in hearing the noise of the vibrator, the rat, having become subjected to hallucinations, feels the shock in its body and experiences pain."

We administered mescaline to rats and albino mice which showed no signs of apparent toxicity until very high doses of more than 300 mg./Kg. subcutaneous were given. Contrarily, the Norwegian piebald rat was found to be particularly sensitive to the drug's action, and the symptomatology observed in this animal recalled the psychopathologic syndrome of confusion seen in man.

The piebald rat, under mescaline, manifested an absolutely typical state of hostility. Moreover, the animals emitted—what is unknown in rats—a sort of continuous growling. We observed strong exophthalmia, abundant salivation, and intense sudation that started in the anogenital region and became generalized. The rat presented a heightened sensitivity to all exterior manifestations, particularly to noise. The administration of low doses of chlorpromazine caused these symptoms to disappear within an hour, the state of excitement and irritability being replaced by absolute calm.

In rats trained to the conditioned reflex by our previously described technique, the state of mescalinization is of special importance. In the untrained animal, as in the conditioned rat treated with chlorpromazine, bell ringing is met with indifference; in the unconditioned rat treated with mescaline, the ringing induced only greater irritability but no apparent hallucinations. In the conditioned rat, however, mescaline provoked a veritable state of dementia. At each ring of the bell, the animal reacted with violent and disordered leaps, sometimes uttering cries, in an attempt to leave the floor of the cage (nonelectrified), as if it were receiving a shock, but making no attempt to climb the rope. Bell ringing thus maintained its value as a conditioning stimulus, except that the reaction was completely disoriented. Moreover, the rat's behavior at the end of the test (6 stimuli in 30 seconds) was that of an animal that has undergone a veritable hallucinatory crisis, shaggy and wet fur, growling, exorbitism, sialorrhea, menacing attitude. With the administration of a low dose of chlorpromazine (1 mg./Kg. subcutaneous), inactive by itself in this test, a complete change of reactions was observed. Not only was the secondary symptomatology inhibited, but the psychic disorientation was corrected and the rat regained its climbing reflex. Further, when the dosage was increased, a state of torpor set in, accompanied by a total deconditioning that was not seen when the same dose of chlorpromazine was administered by itself.

These observations on the animal level are entirely similar to those made in man by Denber and Merlis, who noted that under chlorpromazine there was suppression of mescalinic mydriasis, disappearance of anxiety and agitation, and the appearance of a state of calm, somnolence, and even lethargy.

Following the discovery of the action of the diethylamide of *d*-lysergic acid (LSD 25) on the central nervous system, numerous comparisons were made between this drug and mescaline. Their action in man is similar, but with different points of impact, as demonstrated by the tests of P. N. Witt.[79] The symptomatology of poisoning with LSD 25 is different from that obtained with mescaline. In effect, LSD 25 provokes a rather hebephrenic behavior, whereas mescaline produces a state resembling catatonia.[33, 54] The LSD 25 drug predisposes to euphoria and expansiveness, whereas mescaline produces withdrawal.[13, 67] A comparative study, in animals, of the antagonism of chlorpromazine toward these two hallucinogenic substances would certainly be of interest in our conditioned reflex test, and such a study will be made shortly.

Since 1952, when Cathala and Pocidalo[10] first demonstrated the central action of chlorpromazine, many authors attempted to define the site and mechanism of action of this drug in the encephalon.

Cathala and Pocidalo showed that an injection of 2 mg. of chlorpromazine in the third ventricle provoked a profound narcosis in the dog and suppressed the hypertensive response due to excitation of the central portion of the vagus or to occlusion of the communal carotids. An intravenous injection of adrenalin maintained all its normal hypertensive effects, which demonstrated that the drug did not appear in the blood stream in concentrations sufficient to exercise powerful antiadrenalin action. This experiment was contested by Donnet and co-workers[30] who, utilizing the local anesthetizing properties of chlorpromazine, showed that

the same results could be obtained by placing a tampon saturated with the drug on the floor of the fourth ventricle. These authors thus suspected that, in the experiment of Cathala and Pocidalo, part of the drug injected into the third ventricle was diffused into the fourth, inasmuch as the inhibition of reflexes originating in the sinus persisted after bulbar section.[40]

The sedative effect of chlorpromazine in agitation and in psychoses was interpreted by Lassner[24] as the result of a "pharmacologic lobotomy" interrupting connection between the cortex and the diencephalon. This author also assumed a direct action on the diencephalon in order to explain the blocking of thermoregulation, which otherwise would remain unexplained,[68] as temperature is controlled by the thermoregulatory center of the hypothalamus. This argument loses some of its value if we take into account the work of Giaja,[35] who found that chlorpromazine did not suppress chemical thermoregulation and did not block thermogenesis, although homeothermia was disordered. In effect, chlorpromazine did not provoke an increase in intraorganic oxidations in the rat when the environmental temperature dropped. The animal did not behave as a poikilothermal one, as the drug at most ". . . restricts accommodation to thermogenesis, but does not suppress it."

However, Delay and Deniker,[24, 25] think that the action of chlorpromazine on the diencephalon is probable ". . . by the very nature of the syndromes on which it acts electively."

Terzian[68] for the first time set out to obtain proof of this diencephalic action by studying the electroencephalograms of his patients, trying thus to explain the disinterest caused by chlorpromazine when used alone, the potentiation of the barbiturates when used in combination, and the differentiated action of anesthetics and sedatives. The fundamental result of this study was the demonstration ". . . that the sleep induced by chlorpromazine is absolutely superposable and identical to physiologic sleep in all its phases of depth"; that this sleep can be differentiated in its inductive and awakening phases from barbiturate sleep, and that from this fact ". . . the potentiating action exercised by 4560 R.P. (chlorpromazine) on the barbiturates becomes more understandable."

The electroencephalographic tracings obtained in dogs by Cazzulo and Guareschi[11] also indicated that chlorpromazine engendered a clear sedative and hypnogenic action, and that the latter was intensified with increase in dosage until it reached a state resembling natural sleep.

We note also the work of Hiebel et al[41] who, also with the aid of electrophysiologic methods, attempted to demonstrate and to analyze the site of action and the central mechanism of action of chlorpromazine. These authors showed that "the product depresses the spontaneous activity of the reticular formations of the brain stem and diminishes their sensitivity to afferent sensorial or nociceptive impulses. Chlorpromazine also suppresses the activating effects normally exercised on these formations by circulating adrenalin and by sympathetic discharges linked with stress. Contrarily, the product unmasks the action of certain afferent impulses that inhibit central activity. These three mechanisms produce a continuous depression of a central formation whose important role in the maintenance of the waking state and on the level of motor, sympathetic, and neuro-endocrine activity is well known."

Angeleri et al,[3] following up this type of study, examined the modifications provoked by acoustic stimuli in the mesencephalic reticular formations of the cat treated with chlorpromazine. They found that at this level the product exercised a notable effect, inasmuch as response to afferent excitations was either reduced or abolished, while the sensitive pathways continued to lead excitations to the cortex without change.

Linked with these experiments are the observations of Das et al[16] who studied the effect of chlorpromazine on the electric activity of the isolated cat's brain. They stated: "One is tempted to propose the hypothesis that the central action of chlorpromazine consists in interfering with the controlling influx of the regulatory systems implicating the thalamic system and the activating system of the reticular formation of the lower brain stem, this influence being exercised on the rear area of the cortex, on which afferent impulses must act, thus modifying the states called waking and sleeping."

In a comprehensive work[17–19, 71] that systematically studies, in a variety of tests, all the inhibiting effects of chlorpromazine on motor activity, these same authors observed the action of chlorpromazine on the cortex, on the hypothalamic and medullary reactions and, in general, on all vasomotor reflexes. Since we cannot describe here the details of this important research work, we will confine ourselves to the following essential points: (1) chlorpromazine inhibits motor activity provoked by cortical stimulation and suppresses changes in posture caused by stimulation of the cerebellar cortex, of the cerebellar nuclei, and of the reticular formation.[19] (2) In the absence of central factors facilitating reaction from the spinal cord, its inhibiting effect on the cord's activity is much less pronounced.[19] (3) In decorticated cats, chlorpromazine in low dosage (0.05 to 0.1 mg./Kg.) specifically inhibits tension reactions caused by electric stimulation of sensitive regions of the hypothalamus and mesencephalon, as well as the stimulation of the tensor reflex of the sciatic nerve.[18] (4) In thalamic or diencephalic animals, which present characteristic reflexes for the evaluation of the efficacy of substances with a central action, Werner[71] showed that very low doses of chlorpromazine can produce a considerable and persistent reduction of the tonus of decerebration.

We quote finally the work of R. Wien,[72] who compared the action of chlorpromazine on the reflexes of multisynaptic flexion in cats that were anesthetized, decerebrated, or spinal. This author found that the drug depressed the monosynaptic and flexion jerks in the anesthetized and decerebrated animals, the flexion reflex being depressed more rapidly than the knee jerk. In spinal animals, the reflexes were affected only slightly or not at all, which confirms the results obtained previously.

Fournel[14] found that chlorpromazine diminished respiratory exchange in the nerve cell proportionate to the concentration of the drug in the environment. However, Finkelstein et al[22] showed that the concentrations of chlorpromazine required to suppress the consumption of oxygen in preparations of cerebral tissue were much higher than those that were adequate to obtain an in vivo response in other experiments.

It is undoubtedly difficult to reconcile such opposite results. One might surmise that they would have some connection with possible differences in the ambient medium: it is effectively known that chlorpromazine is soluble only in an acidic medium and is precipitated at

*p*H 7. Whatever the case, it is impossible at the present time to form conclusions in one direction or another.

It is obvious, furthermore, that the results of Finkelstein and his co-workers are in contradiction to the work of Decourt,[20–22] according to whom the narcobiotic action is exercised on all living cells in the following way: (1) it inhibits vital activity; (2) this inhibition is reversible up to a certain point, irreversible thereafter; (3) it can be demonstrated on all living organisms; (4)—and this is of major importance—it has approximately the same quantitative action (for any one product) throughout the entire extent of the living matter.

Berti and Cima,[6] in studying the distribution in tissue of chlorpromazine given subcutaneously to mice, apparently did not find such regular distribution in the various tissues studied (lung, liver, kidney, and brain). The highest concentration seemed to be in the kidney, which, according to the authors, agrees with the slow renal excretion of the product. They add, however, that it is important to note that prolonged action of the drug corresponds to high and diffused concentrations in the various organs, particularly in the brain.

When Agostini and Reda[1] studied whether the phosphatases, which play an important role in the metabolism of the nerve cell, undergo any modifications under chlorpromazine, they noted a very strong increase in acid phosphatase. The authors nevertheless reserved their conclusions, as the observed changes may have been the expression of a general state of toxicity.

The antiemetic action of chlorpromazine toward apomorphine, a central emetic whose action site is in the vagal eminence of the floor of the fourth ventricle, also provides evidence of the double mechanism of this action. In effect, after destruction of this zone, dogs become completely refractory to apomorphine, although they continue to vomit in response to a gastric irritant such as copper sulfate, acting as a peripheral emetic by irritating the nerve endings of the mucosa, thus proving the integrity of the vomiting center.[7, 8, 48] Glaviano and Wang[36] demonstrated that the vomiting center itself is not weakened by chlorpromazine, and that the protective action of the drug was due to a competitive mechanism of receptors in the chemoreceptive emetic trigger zone. Thus the antiemetic action of the drug must be governed by the depressive action exercised on the reticular mechanism of vomiting.

The recent appearance in psychiatry of reserpine, a new medication whose properties, similar to those of chlorpromazine, have paralleled its indication in the same fields, provides a new factor to enlighten the possible mode of action of the two drugs. The two products produce calm and relaxation. They both exercise a certain psychic deconditioning in the rat, which may explain their application in psychiatry. In the laboratory, a potentiating effect on general anesthetics has also been noted with reserpine. Both products provoke a fall in temperature and both affect blood pressure.

However, there are the following differences: (1) the sensitivity of animal species to the two drugs is very different. (2) Installation, intensity, and duration of action are also practically opposed. Chlorpromazine is a compound having a rapid action proportionate to dosage. Reserpine, on the contrary, is not very manageable in the animal, possibly because of its low solubility, which results in a long period of installation. (3) While reserpine in the animal produces a certain potentiation of narcosis, it is interesting to note

that it opposes the analgesic effects of morphine,[61] in contrast with chlorpromazine.[14, 77] (4) Contrary to chlorpromazine, reserpine is neither sympathicolytic nor parasympathicolytic. It exercises no peripheral action nor any inhibitory properties at the level of autonomous ganglia; it is ineffective against convulsant poisons. Workers at present believe that the region where reserpine most probably causes altered balance in the autonomous nervous system is the hypothalamus, where autonomic functions are integrated.

In order to define the sedative action of reserpine, Plummer and co-workers[57] wrote: "According to Hess, sleep is a parasympathetic function caused by a suspension of activity of the sympathetic center in the hypothalamus. Moreover, Hess induced sleep in animals by electrically stimulating the anterior hypothalamic region in the neighborhood of the parasympathetic center. This sleep was accompanied by myosis, bradycardia, and a diminution of peripheral vasoconstriction. It thus appears logical that a drug such as reserpine, which suspends the activity of the sympathetic center of the hypothalamus, should facilitate the establishment of a state of calm. Consequently it is evident that the sedation caused by reserpine is of a different type from that of the barbiturates."

But according to Dasgupta and Werner, although chlorpromazine suppresses the effect of direct stimulation of the hypothalamus and although it is indirectly clear that reserpine exercises a possible depressive effect on the hypothalamus, these two types of action appear to differ absolutely in their mechanism. We might add that reserpine possesses no central antiemetic activity; in certain cases it even acts as an emetic in the dog, probably due to local intolerance.

Although this brief summary permitted a differentiation on numerous points of the mode of action of these two drugs, undoubtedly much remains to be said.[37] We found it of interest to examine their behavior when administered together. In our tests, their action was sometimes similar, sometimes antagonistic. In certain tests (potentiation of anesthetics, hypnotics, or analgesics; antiemetic action), the result obtained demonstrated an antagonism of action between the two products. But in tests on depressive action, as in those of conditioned reflexes, the two products appeared to combine advantageously, the rapid and strong effects of chlorpromazine appearing to be prolonged by those of reserpine.

In conclusion, we note some observations made on man by Staehelin and Kielholz [47, 68] which strikingly illustrate all the symptomatology that has been observed in the animal: "This drug inhibits, both centrally and peripherally, the entire autonomic nervous system. It causes no loss of consciousness; its mechanism of action therefore bears no resemblance to that of narcotics and hypnotics. It plunges patients into a state of calm and relaxation which can best be compared to the phases of hypokinesia, hypobulia and hypophrenia of the diencephalic syndrome of Staehelin or the cerebral psychic syndrome of Bleuler. In addition, one observes a general diminution of somatic functions, and a general inhibition of the psychic efficiency level. The image of the psychic state, i.e. the generalized weakening of will power and impulsion, has been termed by Delay a 'medicated lobotomy'; one could equally term it a reversible medicated inhibition of the diencephalon."

The various laboratory tests on animals provide a fairly faithful picture of the symptomatology seen with chlorpromazine when used in psychiatry. We[69] would also like to

mention the work of Hamon et al[38] and Delay and Deniker[24, 25] who showed the benefits to be drawn from the psychophysiologic "disconnection" effected by chlorpromazine in states of manic agitation. The product induces a state of calm that Delay termed "psychic syndrome of 4560 R.P."* and that Chatagnon[12] considered to be a "transitory psychoplegia." Deschamps[28] described the state of "disinterest in environment" created by chlorpromazine; and the most recent observation of Fabris[31] showed that chlorpromazine induces a "psychic inhibition" and a "psychosomatic rupture" that bring a particularly valuable contribution to the treatment of severe pain, where the psychic element plays a preponderant part in the installation and toleration of the pain itself.

RESUMEN

Esta revisión de las técnicas y métodos de laboratorio demuestra cómo puede estudiarse en los animales las propiedades farmacodinámicas de la clorpromazina. Se empleó mescalina para inducir agitación, agresión y alucinación en algunos animales, observando posteriormente los efectos sedantes de la clorpromazina. Se incluye en este estudio una discusion sobre los diversos modos por los que posiblemente la clorpromazina ejerce su efecto fisiológico. También se realizó un estudio comparativo de los efectos de la reserpina y la clorpromazina, productos estos que parecen combinarse ventajosamente.

RESUME

Cette revue de méthodes de laboratoire et de techniques montre comment les propriétés pharmacodynamiques de la chlorpromazine peuvent être étudiées chez l'animal. La mescaline fut employée pour induire l'agitation, l'agression et l'hallucination chez les animaux, pour ensuite observer l'action sédative de la chlorpromazine. La revue comprend également une discussion des différent points d'impact de l'activité de la chlorpromazine au niveau du système nerveux central. Une étude comparative entre les effets de la réserpine et de la chlorpromazine est rapportée, notant que ces deux produits peuvent se combiner avantageusement.

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Treatment of Mental Disorders with Chlorpromazine

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Until a few years ago, the cerebral cortex was generally believed to be the physical substratum of all mental functions. When the importance of the diencephalon in the function of emotions and instincts was recognized in recent years, this old theory of localization proved to be too one-sided and narrow. Psychiatrists and brain physiologists found that important impulses of instinct and emotion originate in the diencephalon.

Many psychoses and abnormal mental reactions are accompanied by powerful emotional tension, provoking, by way of the vegetative nervous system, somatic disturbances, which, in their turn, make the patient fear that he is physically ill, thus intensifying emotional tension and increasing vegetative disintegration (see figure 1).

The first aim of treatment is to break this vicious circle, which is most easily done by an attack on several fronts, i.e., from the mental and from the somatic side. This is the foundation of Staehelin's basic principle in the treatment of mental disturbances: "Treatment by drugs can only be effective if it is constantly assisted by intensive psychotherapy." Ten years ago, as a result of his experiences in treating patients with diencephalic disturbances, Staehelin understood this vicious circle, and looking into the future, he postulated that new remedies should be developed whose effect should lie between the insufficiently active vegetative sedatives (bellergal, belladenal, and priscophen) and the not entirely harmless "major" methods of psychiatric treatment, such as prolonged sleep, insulin, and electroshock. In our search for a drug of this type, we found that chlorpromazine seemed most likely to correspond to the mode of action postulated hypothetically by Staehelin.

TECHNIQUE, SIDE EFFECTS AND COMPLICATIONS

The technique of treatment with chlorpromazine is handled in different ways according to the nature and intensity of the disease and also according to the various schools of psychiatric opinion. While some psychiatrists prefer "pure" chlorpromazine treatment, i.e., the sole use of the drug, others use it together with barbiturates and other sedatives to induce prolonged sleep therapy. Until now we have avoided the latter method as it did not seem to be more effective and was definitely more dangerous than treatment with chlorpromazine alone. We have, however, in occasional critical moments, added light sedatives (persedon, phenergan, insulin) but not to the extent of inducing prolonged sleep with extinction of consciousness.

The dosage of chlorpromazine must be chosen as individually as possible, according to the prevailing state of the patient. In serious and particularly acute states of disease (acute psychosis), it is absolutely necessary to administer high dosages over a long period. In these cases we inject the drug during a period of 10 days in doses ranging from 150 to 250

mg. per day. Later, we use oral doses from 300 to 400 mg. per day, which are gradually lowered in the course of several weeks or even months. If the risk of relapse appears great (e.g. in improved chronic schizophrenia), we continue treatment, often outside the clinic, with maintenance doses of 50 to 200 mg. A too rapid lowering of doses is often followed by a flareup of the pathologic symptoms.

Smaller doses, i.e., 50 to 200 mg. taken orally, are used for elderly people (with arteriosclerosis), as the time within which the drug is safely effective in these cases is relatively short. Gradually increased doses are recommended in outpatient treatment in order to avoid side effects such as sleepiness and low blood pressure. Fortunately the side effects of chlorpromazine are generally harmless and to some extent they can be avoided altogether.

In the first phase of treatment, the lowering of blood pressure may lead to fainting, particularly in an upright position. Furthermore, various vegetative disturbances, like palpitation and shortness of breath, may occur during treatment. If high doses are given, one may occasionally observe parkinsonian symptoms, i.e., tremor, masklike face, salivation, and akinesis. These disturbances can, however, be reduced to a great extent by antiparkinsonian drugs, and they disappear spontaneously when the dosages of chlorpromazine are lowered. The diencephalic effect of the drug is shown in many patients by a sensation of voracious hunger, followed by a considerable increase in weight, which in some cases may amount to veritable adiposity.

The most unpleasant side effects consist of allergic affections of the skin and, in some cases, jaundice. Allergic trouble occurs in the form of generalized rashes, urticaria or Quincke's facial edema. Many patients under chlorpromazine treatment developed a particular susceptibility of the skin to solar irradiation. A much more resistant kind of trouble is presented by the allergic reactions, mainly eczematous, acquired through contact with the drug by the nursing staff, which, fortunately, rarely occurs in a serious manner.

ADDITIONAL EMOTIONAL TENSION
EMOTIONAL TROUBLE (CORTEX)
ACCUMULATION OF EMOTIONAL TENSION (AS A CONSEQUENCE OF INCREASED SENSITIVENESS AND TENDENCY TO DYSPHORIC STATES)
FEAR OF PHYSICAL ILLNESS
DYSTONIA
VEGETATIVE CENTERS (DIENCEPHALON)
SOMATIC VEGETATIVE DISINTEGRATION (CIRCULATORY, GASTROINTESTINAL DISTURBANCES, AND CEPHALEA)
INCREASED IRRITABILITY, EXCITABILITY, AND FATIGUE
INCREASE OF VEGETATIVE
SLEEP DISTURBANCE (LACK OF SLEEP)

FIG. 1. Vicious Circle in Mental Disturbances.

TABLE I

Classification of 205 Patients with Schizophrenia According to Duration of Illness.

Duration of illness (years)	Number of patients	% not improved	% slightly improved	% improved	% socially cured and full remission
0 to 1	53	6	—	21	73
1 to 5	46	11	—	48	41
over 5	106	16	26	40	18

The side effect most to be feared is certainly jaundice, which has been observed in our clinic as well as in other mental hospitals. We have seen 11 cases (3 per cent) of jaundice among 394 cases treated with chlorpromazine during the period from February to October, 1953. Usually the complication arose during the first 30 days of treatment. The cause of jaundice is supposed to be a disturbance of the bile ducts. We succeeded in limiting the appearance of jaundice in several cases by administering a cholagogic drug. Since we have given choleretic drugs prophylactically (one tablet of felamin three times during the first six weeks of treatment), only exceptional cases of jaundice have been observed. The blood count often presents leukocytosis during treatment. At the same time the erythrocyte sedimentation rate is often distinctly accelerated. Agranulocytosis was never observed.

In approximately 1000 patients whom we have treated with chlorpromazine to date, only one death occurred that was possibly connected with the medication. This was a sudden embolism of the lung, caused by severe thrombosis of the iliac vein.

SCHIZOPHRENIA

A number of papers have been published about the treatment of schizophrenia with chlorpromazine. The results given differ; in particular, authors do not seem to agree whether certain symptoms only of this disease can be improved or whether a fundamental control can be exerted over this psychosis.

We have observed the effect of the drug on a group of 205 schizophrenics with varying duration of illness over a period of 11 months. All these patients were treated solely by chlorpromazine therapy with an initial series of injections. Additional methods of treatment were only used with these patients to an extent that is negligible for the therapeutic result. The length of treatment depended on the seriousness of each case, ranging from one to several months.

The 205 cases of schizophrenia were divided into different categories according to duration of illness (see table I).

No conclusive proof can be gained by considering cases with a short duration of illness, i.e., up to one year, as patients in this category show a tendency to spontaneous improvement and remission. Still, it is evident that the greater part of these cases achieved remission. The question whether an acute phase of schizophrenia can actually be shortened or whether it is only "covered up," cannot be decided at present. In many cases it is quite obvious that the drug only suppresses the symptoms, which appear again if dosages are reduced too soon.

The great advantage of chlorpromazine treatment in acute mental disease lies in the possibility of calming patients very quickly. Acute states of excitement and anxiety, often connected with suicidal and aggressive tendencies, frequently calm down under the effect of the drug in the course of a few days or even hours. Even the shock of hospitalization, which often seriously affects the patient, can be alleviated by the immediate institution of treatment.

Favorable results are particularly striking in schizophrenias of one to five years' duration. In this group we see mostly cases that still show the signs of active disease, but that have already entered into a chronic stage. These cases are known to have a poor chance of spontaneous recovery; even with the customary methods, i.e., electroshock and insulin therapy, temporary improvement of short duration was often all one could obtain. With chlorpromazine treatment we have been able to influence very favorably a considerable number of these subchronic cases, among them quite a few who, previously, had responded only very slightly or not at all to other methods of treatment. The result is particularly impressive in patients with periodically exacerbated catatonic states. While these patients could only benefit from electroshock therapy insofar as remissions of short duration occurred, chlorpromazine treatment produced remissions extending over months or even years.

In schizophrenics who have been ill for more than five years, essential improvement or even remission was considered almost a miracle until now. With the help of chlorpromazine, however, considerable improvement was obtained even in a fair number of these cases, although the beneficial effect varied in degree in individual patients. In some cases, treatment merely succeeds in calming the patient or in eliminating stereotyped behavior, mannerisms, or aggressiveness. In other patients, important emotional relaxation or even reorganization of the entire personality was achieved.

In chronic cases, it is unavoidable to administer treatment over a long period and to continue it with a maintenance dose. Lack of success with a short treatment is no reason for disappointment and loss of courage. In many patients, improvement only manifests itself after several months.

Chlorpromazine treatment is particularly apt to influence in a striking manner the schizophrenic disturbances of thinking. In many cases, incoherent thinking became well ordered again. Though emotional changes tend to improve more slowly, considerable normalization of emotional contact can be observed in many patients under the influence of the drug. We must, however, stress the necessity of submitting improved chronic schizophrenics to thorough psychotherapy and of giving them any social assistance they may need.

Among subgroups of schizophrenia, the catatonics and paranoics were those who benefited most from chlorpromazine. Delusions and hallucinations lost their intensity during treatment; they became less agonizing for the patient and, in quite a few cases disappeared completely. The effect of the drug is less favorable in hebephrenia and in schizophrenia simplex with a tendency to slow deterioration. Quite generally we observed that treatment was most successful in those patients whose personality was well preserved before chlorpromazine was given.

The administration of maintenance doses often helps to keep up the level of improvement

attained in chronic cases, though in some patients relapses may occur in spite of continued medication. Very often, however, a relapse was proved to be due to carelessness of the patients who no longer followed the medical instructions and who neglected their medication. Once a relapse had occurred, renewed treatment, however, soon helped to re-establish the former state of improvement.

Summing up, the greatest advantages of chlorpromazine treatment of schizophrenics seem to consist in its rapid calming action in states of acute excitement, in producing relaxation and improvement even in chronic patients after many years' illness, and in the possibility of treating patients who are threatened by relapse over a long period, even outside the clinic, with small maintenance doses. If chlorpromazine treatment is insufficient as a basic therapy, other methods of therapy (insulin, electroshock therapy) can be added without any difficulty once the initial phase of treatment by injections is over. The most spectacular consequence of treatment may be seen in the change of the atmosphere of a mental hospital, where, because of the new drug, a pleasant calm reigns even in the worst "restless" wards.

DEPRESSIVE STATES

In reactive depressions, drug treatment can be avoided as a rule. We think that these patients should be almost entirely the object of psychotherapy.

Neurotic anxiety associated with depression, i.e., depressive states that arise in the course of a neurotic development, are only treated by us with drugs if the vicious circle, explained in our introduction, has obviously become fixed. This is the case in those depressive neuroses in which anxiety and vegetative disintegration so much predominate that they distract the patient's attention from psychotherapy or render the psychotherapist's attempts difficult or impossible in other ways. The vicious circle should then be broken by drug therapy so that analytic work is no longer constantly disturbed.

In neuroses of this kind, chlorpromazine has proved to be a valuable help. Restless anxiety and vegetative disturbances can be calmed by the drug in such a manner that the neurotic manifestations can be subjected to psychotherapy quietly and without risking complication by attacks of panic.

Unfortunately endogenous depressions do not react as favorably to chlorpromazine as we had originally hoped. In cases where agitation and anxiety are the main features, the depressive symptoms can be slightly alleviated, so that patients feel calmer, more relaxed, and capable of gaining some distance from their depressive delusions. Suicidal impulses also are diminished and lose their importance. For patients with melancholia and mainly hypochondriac manifestations, the lowering of the entire level of psychic energy caused by chlorpromazine is occasionally an unpleasant experience, as their torturing ambivalence and the inhibition of volitional impulses are rather increased by it. Comparative studies of the course of periodic melancholia in the long run have shown that it is impossible to shorten the phases of disease with chlorpromazine.

A significant improvement of depressive states can often be achieved by combining chlorpromazine with electroshock therapy, which we always give with pentothal narcosis and under the protection of curare. With this method, one succeeds in reducing anxiety, the

torturing depressive delusions, and the risk of suicide until, with the help of electroshock therapy, a partial remission is achieved, and the patient is ready to leave for home. We have not been able to lengthen the free interval by continued medication.

All the symptoms of the manic phases of manic-depressive psychoses can be sufficiently toned down by chlorpromazine so that patients do not cause much trouble to the nursing staff, and occasionally they can be induced to do regular work. Although the patients may be euphoric, easily excited, and diverted, they can be guided and influenced with less difficulty. We, therefore, think that in this new drug we have found an appropriate and efficient remedy for toning down manic states.

TOXICOMANIA

In the treatment of toxicomania (addiction to morphia, hypnotics, sedatives, and analgesics), the drug has its value for starting withdrawal, as well as for aftertreatment. By a combined cure with insulin and chlorpromazine, the agonizing symptoms of abstinence can be avoided to a great extent. With the help of small insulin doses given three times a day, a state of relaxation and somnolence, accompanied by slight perspiration and stimulation of appetite, can be induced. In order to suppress the withdrawal symptoms completely, the patients are given, beside the insulin treatment, three doses daily of chlorpromazine, which has a sedative effect on central as well as peripheral vegetative mechanisms. As abstinence symptoms are mainly caused by the disintegration of the vegetative nervous system, this procedure is very apt to avoid them altogether. We have carried out this combined withdrawal treatment successfully in more than 100 cases of toxicomania. After the actual detoxication, which lasts for two to three weeks on the average, we continue chlorpromazine during the phase of psychotherapy that aims at getting to the roots of toxicomania. The generally sedative effect of the drug on vegetative and mental functions helps to maintain in patients an emotionally settled, relaxed, and calm state and to conquer their difficulties in finding sleep, which often cause serious trouble. In this way, the urge for renewed stupefaction or relief by drugs loses its intensity and can be more easily resisted, which is very important in reducing the risks of relapse.

CHLORPROMAZINE TREATMENT IN OTHER PSYCHOTIC STATES

Our experience with chlorpromazine in other psychoses is limited. It seems that the indication for the drug is favorable in hyperkinetic phases of diencephalic disturbances ("Diencephalosis") described by Staehelin. Above all, the vegetative symptoms, which often occur with great vehemence in these phases, can be quickly eliminated.

A good reaction to chlorpromazine was noted in erethistic mental defectives, who, of course, need permanent medication.

The effect of chlorpromazine also seems to be of special advantage in confusional states in senile or arteriosclerotic psychosis. Under the influence of the drug, confusion and anxious agitation disappear, and in many cases it is possible to establish a normal day-night rhythm. Very often one can even dispense with barbiturates, which in elderly people often increase confusion.

We have also observed gratifying results with chlorpromazine in exceptional states of epileptics and in periods of restlessness after cerebral trauma.

As might be expected, no alteration of the abnormal personality structure was obtained with chlorpromazine in psychopaths; on the other hand, we succeeded in reducing certain abnormal mental reactions (hysteric and paranoid) in these patients.

In the treatment of neuroses and psychosomatic affections chlorpromazine is a very useful remedy, particularly if vegetative symptoms accompany the mental disturbance. It must be noted, however, that the cure of these diseases must not be expected from medication alone, but from a combination of drug treatment and psychotherapy. In neurotics, chlorpromazine often helps to render them accessible to psychotherapy. We have reached remarkable results with the drug in anxiety neuroses and hypochondriac neuroses; one case of long-standing bronchial asthma was improved, at least temporarily. In obsessional and compulsive neuroses, we observed a lowering of emotional tension, although obsessive thoughts were not considerably reduced during the treatment.

RESUMEN

Se describe la técnica, reacciones secundarias y complicaciones del tratamiento con clorpromazina. Este estudio registra los resultados favorables obtenidos en ciertos casos de esquizofrenia aun en los de larga duración. La clorpromazina ha producido resultados benéficos en la mayoría de los pacientes catatónicos y paranoicos, no siendo efectiva en los estados depresivos pero sí de valor en algunos tipos de depresiones neuróticas. Tambíen es de utilidad en el tratamiento de las toxicomanías durante la fase de interrupción del tóxico. Otros estados psicóticos que se beneficiaron con la clorpromazina fueron las alteraciones diencefálicas, estados seniles de confusionismo y algunos estados post-epilépticos o post-traumáticos.

RESUME

Cette étude décrit le mode d'emploi, les réactions secondaires et les complications dans le traitement par la chlorpromazine. Elle note que de bons résultats ont été obtenu dans certains cas de schizophrénie, même de longue durée. Les états de catatonie ou de paranoide ont été spécialement bénéficiés. Le médicament ne fut pas aussi éffectif dans les états dépressifs, quoiqu'elle a beneficié certains types de dépression névrotique. Elle a également bénéficié le stage de retirement dans les toxicomanies. Quelques autres états qui ont bénéficés de la chlorpromazine étaient des désordres diencéphaliques, les états de confusion de l'âge, et des conditions post-épileptique et post-commotionel.

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Chlorpromazine Treatment of Hospitalized Psychotic Patients

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Experience has more than justified the early optimism of reports on the effectiveness of chlorpromazine in the treatment of mental illnesses, but it has also brought a greater understanding of the relationship between drug therapy and other components in the work of readaptation, education, and rehabilitation of the mentally ill. It has become evident that much of the past effort in psychotherapy and re-education of psychotics without preceding or concurrent organic treatment (which includes insulin, electroshock, and "psychosurgery," as well as drug therapy) was like starting reconstruction during the active period of a catastrophe such as a major flood or fire, when the activity of reconstruction might itself obstruct the successful outcome of the battle. All of this has become clearer with the development of new insights into the psychotic processes during drug treatment of patients.

The experience reported here was derived from treating approximately 1500 hospitalized patients with chlorpromazine and more than 500 with other drugs, chiefly reserpine. The latter group, however, will not be discussed, except where the work relates to that with chlorpromazine in some manner. Most of the patients were from Longview State Hospital, and about 75 per cent were ill for more than five years. It is tentatively useful to subdivide the patients into three groups: acute, ill for two years or less; subacute, ill from two to five years; and chronic, ill for more than five years. This will be attempted as much as the available data will permit in the description of results. The age groups studied are those of the psychotic population of a state hospital and of a general psychiatric practice, with a predominance of the third to the sixth decades. Sexes are about equally represented. Thorough sifting of the data for results by age and sex indicates clearly that age and sex are of no importance to the problem at hand. Most of the patients were suffering from schizophrenia, particularly in the more chronic group, with affective psychoses and organic brain syndromes following in order of numbers treated.

METHODOLOGY

Although chlorpromazine can be given orally or parenterally, the parenteral route is used only in uncooperative patients. The parenteral solution of chlorpromazine is irritating, and the maximum dose tolerated in a single injection is usually considered to be 100 mg. The injection is less painful and more quickly absorbed if the drug is diluted with equal parts of physiologic saline and 0.1 to 0.2 cc. of hyaluronidase solution (as usually prepared for hypodermoclysis) is included in the injection. By this means, as much as 200 mg. may

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From the Longview State Hospital; E. A. Baber, M.D., Superintendent.

be administered at one time, 100 mg. in each gluteal muscle mass, and the dose repeated at four to six hour intervals for three to five days. If the most recalcitrant patients (we have seen only 2) persistently refuse medication by mouth, even under the influence of injected chlorpromazine, such patients can be given larger doses of chlorpromazine by gavage two or three times daily. With the larger doses thus achieved, the patients have become tractable, amenable to reason and discussion, and have been persuaded to swallow the beneficent tablets.

Oral and parenteral medication is usually begun with 50 mg. doses given every six or eight hours. Older or physically debilitated patients may be started with 25 mg. doses, and individuals over 70 years old are often given 10 mg. doses. Experiments with doses of 5 mg. have not been particularly rewarding. After two to seven days, depending on necessity and response to the drug, the individual dose is increased to 100 mg. (three or four times daily). Thereafter, the dose is increased until some response in the form of change in psychotic manifestations or severe side effect is produced. The maximum useful dose in most patients is 500 mg. four times daily. Rare individuals tolerate and derive benefit from more.

Children in the hospitalized psychotic group have tolerated proportionately equal amounts of chlorpromazine, with initial doses of 10 or 25 mg. three times daily.

The treatment is continued at the maximal level for varying periods; in some patients recently ill, for four to eight weeks; in patients with chronic illness of more than a year's duration and in some of recent origin, treatment is required for many months or even indefinitely. In some chronic psychotic patients, benefit does not seem to accrue until treatment has been given for 6 to 10 months. In the chronic group particularly and in many of the acute and subacute psychotic states, less than two months of treatment should not be considered a fair trial of the method. This experience is analogous to that with electroshock in which persistent treatment is often needed to achieve recovery and prevent relapse.

The physiologic effects of chlorpromazine are important in the clinical management of medication. Within 24 hours, often after the first dose of the drug, the patient becomes drowsy and lethargic. This somnolence is different from that produced by barbiturates in that the patient can be readily aroused and maintains a clear sensorium with adequate motor coordination. A patient who is apparently deeply asleep will respond readily when aroused and will be able to answer questions sharply, take care of himself, keep himself clean, dress, and control excreta. With similar somnolence from barbiturates, marked sensorial, motor, and social disorganization would be evident. The drowsiness usually subsides after 3 to 10 days while medication is continued, particularly if the patient can be given some duty or engaged in some useful interesting activity. Patients report that, in spite of somnolence, there is an improvement in their ability to remember and perceive the content of reading material, they do better school work (even though they might occasionally fall asleep in class), and they finish physical tasks more rapidly. This is undoubtedly the result of diminished distractibility from both internal and external sources.

The drowsy and lethargic state may frighten the uninitiated physician or nurse and frequently arouses anxiety in relatives. It is usually best to accomplish the early phases of

treatment in hospital surroundings, particularly with psychotic patients having over-anxious families. Some patients, not nearly as many as the earlier literature indicates, develop vascular hypotension. As will be indicated later, less than 2 per cent of the treated patients require special management for hypotension. The hypotension is always orthostatic, and it is immediately relieved by assuming the recumbent position. In most patients, this state subsides within a few days and does not interfere with an increase in dosage. It is wise, however, to relax strict ward routines and allow patients to lie down, nap, and rest as they please. Experienced nurses and attendants usually note that these side effects are minimized when patients eat adequately and the oral medication is given after eating. Patients who do not swallow the medicine, but secrete it in a corner of the mouth or under the tongue and then dispose of it, show none of the evidence of chlorpromazine effect. With adequate observation of individual patients, appropriate change to parenteral medication can be instituted with a minimum waste of time.

RESULTS AND DISCUSSION

The most dramatic effects of chlorpromazine are seen in patients suffering from delirium. This may be the result of long-continued alcoholic excess with the typical picture of delirium tremens or acute hallucinosis, or it may be a manifestation of an acute schizophrenic or a schizoaffective state, which is often called catatonic excitement. In the alcoholic deliriums so frequently accompanied by hallucinations of animals, the patients, often within two or three hours and practically always within 24 hours, have lost the hallucinatory manifestations, whether they be snakes, oddly colored giraffes, or, as one patient described them, "fish worms crawling on my fingers." With the disappearance of hallucinations, other clinical manifestations of the alcoholic delirium also subside; tremulousness and anorexia are relieved and adequate muscular control and appetite are restored. With this change, insight is often developed into the mechanism behind the patient's drinking, which renders further management more successful. As with all severe disturbances resulting from alcohol, nutritional aspects must be managed with adequate diet and large doses of vitamins, even with the help of chlorpromazine.

Acute Schizophrenic Psychoses. Patients with overwhelming paranoid delusions and threatening hallucinations are often extremely combative and resistant to any kind of management. Such patients are often brought to a hospital in maximal physical restraint and show maximal hostility and combativeness. The intensity of this kind of reaction subsides within hours, and usually within 24 to 48 hours such patients may be allowed out of restraint or seclusion and become cooperative helpful individuals. In the subsidence of the extreme psychotic manifestations, there often occurs a recapitulation in reverse of the development of dynamics and manifestations of the psychotic state.*

* An example of this is the patient who came to the hospital with four deputy sheriffs barely in control of the situation. He was loudly shouting his determination to kill. Within 24 hours, under the influence of chlorpromazine, he became quiet and could be allowed out of restraint. In three days he was helping serve meals and carried out other minor ward tasks. When he appeared at a staff conference after four days of treat-

(*Continued on next page*)

TABLE I

Therapeutic Results in Schizophrenia of Recent Origin
Treatment Period of 1 Month to 8 Months
(1953, 1954, 1955 Admissions)

Classification of results	Number of patients
A	31
B	31
C	35 (20)*
D	6 (5)*

* Figures in ( ) indicate treatment of two months or less.

In the patient with acute psychotic states of recent origin, the problem of rehabilitation and return to social usefulness and acceptance is usually relatively easily solved by his return to his former occupation and social status where his acceptance by employer, family, and friends is all that is necessary to achieve resumption of normal activity.

Table I indicates what may be achieved in schizophrenic psychoses of recent origin when adequately treated with chlorpromazine. The results are graded as follows: (A) Patients who have recovered from all active psychotic manifestations, particularly those who have lost all delusions and hallucinations, have insight into previous delusions and hallucinations; have adequate affect, social, and industrial adaptive capacity, equal at least to the premorbid level; and have no overt hostility, particularly to the hospital or its staff. (B) Individuals who have recovered from most psychotic manifestations, but who may not have lost belief in previous delusional experience, who are able to make a satisfactory social and industrial adaptation away from the hospital or in the hospital under privileged conditions, and whose improvement may be summarized as "a good social remission." (C) Patients who have improved from the initial condition in significant ways, particularly in the ability to communicate verbally; in diminution or absence of assaultiveness, incontinence, denudativeness, and other gross manifestations of psychosis; and in some diminution of psychopathologic manifestations such as delusions and hallucinations, without actual resolution of these. (D) Patients who have improved only slightly or not at all.

The treatment of acute psychotic states has become a more rewarding element of private practice, since it can be successfully achieved in the psychiatric departments of general hospitals where patients can be rendered manageable in a relatively short time and where acceptability under conditions of general hospital management is no longer doubtful. The duration of hospitalization is markedly reduced, so that many patients who would previously have required several months of hospitalization now require no more than two to

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ment, he had the appearance not of a wildly excited, homicidal psychotic, but of a whimpering, anxiety- and guilt-ridden psychoneurotic. Within a few weeks, he was able to understand the origins of this state in his reaction to a demanding, exploiting parent who had prevented the patient's achievement of normal forms of gratification by excessive demands for attention, service, and substance. Such recapitulation in reverse of the dynamics and mechanisms of psychotic development is in itself helpful to the patient for the development of insight under sympathetic psychiatric guidance. Haste and urgency on the part of the psychiatrist in the management of such states can be productive of harm, just as it can be without the use of chlorpromazine.

four weeks. Statistics that can be adduced at this time cannot demonstrate this point adequately, since, for purposes of study during the first 12 to 18 months the drug was used, patients were kept under close surveillance for longer intervals, so that the shortened hospital stay is only recently evident in the monthly reports.

Chronic Schizophrenic Psychoses. In the treatment of these patients under state hospital conditions, the achievement of adequate results depends on the integrity of the personnel who administer treatment and unremitting persistence with adequate amounts of the drug. Particularly in the chronic psychotic individual are results of palliative as well as curative degree significant. Table II indicates the numerical results in a group of chronic schizophrenic patients long resident in Longview State Hospital. Treatment of such patients represents a different problem from that presented by those with an illness of recent origin. In chronic illnesses immediate effects of the drug often fail to appear, except that the patient may be made drowsy or may in the course of several weeks begin to show signs of extrapyramidal neurologic effects.

Dosage in chronic patients must usually be at higher levels, 1200 to 2000 mg. per day in three or four doses. The development of side effects, particularly the neurologic effects, must not be considered an indication for stopping treatment. In the occasional chronic and severely disturbed individual, who was more or less continuously in restraint or seclusion before chlorpromazine, electroshock treatment may be given concurrently with the drug. As with more acute illnesses, electroshock is more effective, and fewer treatments are needed to produce benefit when chlorpromazine is given concurrently.

Delusional and schizophrenic-type of thinking and judgment may persist for some months, in spite of the obvious physiologic effect of the drug. However, after periods of one to six months or even longer, the delusional material disintegrates, the patient no longer perceives hallucinations, and he often seems to develop some degree of insight.*

TABLE II

Therapeutic Results in Chronic Schizophrenia

Classification of results	Continuously in hospital							
	0–10 years				Over 10 years			
	Months treated				Months treated			
	1–2	2–4	4–8	8 plus	1–2	2–4	4–8	8 plus
A	2	2	14	15	0	0	1	0
B	6	10	45	10	0	3	3	1
C	23	15	55	10	11	23	34	4
D	6	4	9	0	9	41	6	0
Total	226				Total	136		

In this table, the period of treatment is indicated. The data show that more patients improve as the period of treatment is prolonged.

* In such patients, for example, delusions of being royalty disappear, and the erstwhile royal duchess becomes willing to help with the kitchen tasks on the ward; persecutory delusions are given up because they are recognized in the patient's words as "stepping stones to insanity"; and voices cease to be heard and are explained by the statement "they must have come from my imagination."

TABLE III

Schizophrenic Patients Who Had Previous Lobotomy (One or More Times) Treated with Chlorpromazine More than One Month

Classification of results	Continuously in hospital	
	0–5 years	Over 5 years
A	0	0
B	7	8
C	11	38
D	2	11
Total	20	57

Such improvement must be considered only a mandate to further activity in re-education, rehabilitation, and cautiously directed psychotherapy. Medication must in practically all instances be continued, as far as we can tell, for an indefinite period, sometimes with continued dosage at a relatively high level (400 mg. three or four times daily), but often at a gradually diminished level (50 to 100 mg. three or four times daily) after several months of treatment. Such results are achieved even in patients who have been subjected previously to intensive treatment with insulin, electroshock, and lobotomy. Lobotomies are, therefore, no longer to be considered a final desperate measure.

Table III shows results that can be obtained in a group of patients who have been previously subjected to lobotomy. In Longview State Hospital, lobotomies are done only after extensive treatment with electroshock or insulin failed to produce an improvement. An appreciable number of patients can be brought to a useful level of functioning after previous failure of even the most drastic kind of therapy when chlorpromazine is administered persistently.

Besides the patients who benefit to the degree that they can be rehabilitated completely, a considerable group, actually the majority of patients in the chronic group, are relieved of the most serious psychotic manifestations and can usually be made useful, ceasing to be sources of violent difficulty. Assaults, destruction of property, soiling, and denudativeness diminish, so that restraint becomes an infrequent and always transient necessity, seclusion can be abolished, and so-called "violent wards" cease to exist. Table IV indicates an example of this in the daily average of patients restrained on the male "violent ward" with a change obviously taking place as the result of treating about one-half the patients with chlorpromazine. Such wards may now be decorated with vases, pictures, drapes, and unprotected television sets and radios. The patients who were previously most destructive are in many instances the most protective of such property and the most helpful in assisting with housekeeping tasks, errands, and the management of newer, less well-adapted patients.

The changes in previously resistant, disturbed, and violent patients lead to changes in the functions of attendants, psychiatric aides, nurses, and physicians. Attitudes of resentment and even hostility give way to friendly interest that expresses itself at times in ways previously unheard of, such as staff members purchasing material for recreational activity that was not obtained promptly enough through the usual hospital channels, and personnel

inviting patients who were serious management problems for outings, when families of the patient are not available or are unwilling to accept as real the metamorphosis in behavior. Group recreational activities can now be taken over by attendants, and certain aspects of re-education can be initiated by nurses. Physicians whose previous efforts were limited to the signing of restraint orders and prescribing sedation, now find themselves taking part in a growing psychotherapeutic program. It cannot be emphasized strongly enough that psychotherapy with such patients must be a cautious process about which premature discussions should be avoided, since they would only re-enforce the hostile and dependent patterns of behavior.

Table V indicates the previous experience over a period of about 16 years with electroshock and insulin treatment of schizophrenic psychoses in state hospital patients comparable in every way to the chlorpromazine-treated group. The patients hospitalized for one year or less are comparable with the acute schizophrenic group, and those hospitalized for more than one year, with the chronic group. It is evident that chlorpromazine compares favorably with these previous groups and, particularly in the chronic group, far exceeds electroshock treatment in effectiveness at a palliative level.

Manic-Depressive Psychoses. Excitement and overactivity are quickly reduced with a few injections of chlorpromazine; further subsidence of the psychosis occurs with continued oral medication. The actual manic process, however, does not subside as rapidly as does the patient's overactivity. Even in the initial period of drowsiness characteristically produced by chlorpromazine, the patient when aroused to conversation, continues for some time to show hyperbolic associations, punning, rhyming, and alliteration, but without the motor excesses. Continued treatment over a period of weeks in most patients causes the manic psychosis to subside completely at about the same rate that would be achieved by electroshock treatment necessary for such psychosis.

Depressed states sometimes respond similarly to chlorpromazine, with reduction in anxiety, self-disparagement, and nihilistic feelings, but unfortunately most depressive patients do not show such improvement, and many even show accentuation of depressive manifestations. However, if such patients are put under the influence of chlorpromazine and given electroshock therapy concurrently, it is found that the electroshock is more effective than it would be without chlorpromazine; fewer treatments are needed, and the

TABLE IV

Restraint Experience on Male "Violent" Ward

		Monthly average, patients/day			Monthly average, patients/day
1954	March	11.6	1954	November	12.1
	April	11.7		December	10.5
	May	12.7			
	June	14.0	1955	January	6.3
	July	13.6		February	5.9
	August*	11.1		March	4.1
	September	12.2		April	1.4
	October	14.0		May	>1.0

* Chlorpromazine started.

TABLE V

Comparison of Therapeutic Results in Schizophrenia

Classification of results	Insulin (with and without electric treatment)		Electric treatment		
	Years in hospital		Years in hospital		
	0–1	1–10	0–1	1–10	Over 10
A	35	8	23	3	1
B	67	31	72	23	3
C	33	31	52	33	12
D	17	17	22	7	6
Totals	152	87	169	66	22

intervals between treatments may be lengthened. This has been observed repeatedly in patients who have had treatment in the prechlorpromazine era and have had relapses since chlorpromazine became available. The treatment of such patients is gratifying; they appreciate not having to take as many electroshock treatments for relief from their symptoms, because little or no confusion develops with fewer electroshock treatments, and there is often an improved capacity for the development of insight into the mechanisms of psychoses. In no instance have we found any difficulty resulting from the use of electroshock while patients were under treatment with chlorpromazine, even in amounts of 1200 or 1500 mg. daily. More than 1000 treatments have been given to more than 100 patients with no adverse effect. In our opinion, the reports of acute hypotensive reaction, vascular collapse, and even death in patients treated simultaneously with chlorpromazine and electroshock require more satisfactory description. In the instances in which this has been possible, the drug has always been exonerated.

Table VI points out an important aspect of the effectiveness of chlorpromazine in reducing the rate of relapse in patients who have been released on "convalescent status." Over an eight month period, patients released from the hospital after treatment with chlorpromazine are compared with those treated by other methods, chiefly electroshock. The difference in the rate of return to the hospital, indicating a relapse, is impressively in favor of chlorpromazine. This experience has led the social service supervisor of patients on convalescent status to request chlorpromazine treatment for such patients when there is evidence of the return of psychotic symptoms before the symptoms have become so severe that the patient's return to the hospital is necessary. It should also be indicated that the rehospitalization of chlorpromazine-treated patients is in almost every instance the result of discontinuing or refusing medication.

Chronic Brain Syndromes. In recent years, chronic brain syndromes associated with senility and cerebral arteriosclerosis have represented an increasing and important proportion of admissions to mental hospitals. Patients with such illnesses have been considered untreatable and hopeless. Since chlorpromazine has been available, however, many of the important symptoms of organic disturbance—agitation, anxiety, restlessness, sleeplessness—have been found susceptible to partial or complete relief from chlorpromazine. Much smaller

doses are used in older individuals, particularly initially, and increases in dosage are carried out slowly to full therapeutic effect. The usual starting dose is 10 or 25 mg. three times daily. In older individuals with serious or potential cardiovascular defect, intensive medication may produce hypotension, to which the cardiovascular system can no longer adapt itself adequately, with danger of producing local ischemic states inconsistent with survival. No dangerous side effects have been encountered with a low dosage of chlorpromazine, and the benefit of medication, even to the point of social recovery and return to family living, makes trial medication mandatory. Chlorpromazine, however, cannot be expected to cure or slow the progress of the aging process and its components.

Huntington's chorea, which has been resistant to any form of treatment until the recent introduction of procaine amide, has been found susceptible to chlorpromazine. Chlorpromazine produces a greater degree of relief from chorea than does procaine amide and more relief for the anxiety that is the major component of psychotic manifestations. However, advanced sensorial change associated with chorea of long duration does not improve with medication. It is too early to state whether the advance of organic deterioration is slowed by this medication, but for the first time such patients have been able to return to their homes and lead useful lives with minimal limitations in some instances.

COMPLICATIONS AND SIDE EFFECTS

Table VII shows the clinically important side effects and complications of treatment with chlorpromazine. Minor side effects such as somnolence and lethargy are usually transient and are usually manageable by manipulating the dosage. It must be understood by the physician and the patient that recovery from a serious illness such as a psychosis may not be comfortable or pleasant in all instances, just as recovery from surgical operations is usually uncomfortable and painful before the benefits of the procedure are achieved.

Dermatologic manifestations, particularly the various kinds of eruption, are managed by the administration of antihistamine in adequate amount, by reduction in dosage of chlorpromazine, or both. In rare instances a rash is severe enough to require cessation of the drug for a few days and then resumption at a lower level with more deliberate increase in dosage. In such cases, a few doses of ACTH gel, 20 to 40 units once daily, may also be given. This treatment is effective regardless of the form that the eruption may take. Reactions resulting from photosensitivity are different from other eruptions and are particularly common in the summer months. These are limited to the exposed areas of the body and always appear as exaggerated types of sunburn. It is questionable whether the drug must

TABLE VI

Convalescent Status Record
(August 1954 to April 1955)

	Placed on convalescent status	Returned from convalescent status
Nonchlorpromazine patients	171	59
Chlorpromazine patients	93	6

TABLE VII

Complications and Side Effects of Chlorpromazine (Severe Enough to Require Treatment) Among 1227 Patients Treated

	No. of patients	Per cent
Dermatologic effects	141	11.4
Hypotension	18	1.5
Parkinsonism	276	22.5
Jaundice	5	0.4
Agranulocytosis	4	0.33

be withdrawn, although in severe types of sunburn withdrawal is necessary more for the morale of the family and attendants than for recovery from the condition. Itching associated with photosensitivity is relieved with antihistamine and severe types of sunburn are treated with small doses of ACTH, preferable in the slow-acting form so that only one injection daily need be given. The usual dose is 30 to 40 units of the gel once daily for two or three days. If extensive areas of the body are involved with blistering, treatment is carried out in the same manner as for any other severe burn, with local dressings, replacement of plasma protein, and antibiotics to prevent infection.

Parkinsonism is a frequent effect of long-continued administration of large doses of chlorpromazine, particularly if it is carried out in chronic psychotic illness. The parkinsonism must not be considered an indication for the interruption of treatment. At times, some reduction of dosage is necessary, but the manifestations are most readily controlled by the use of an antiparkinsonian drug. In our experience, methane sulfonate, 1 to 2 mg. two or three times daily, has been found very useful in overcoming the manifestations of parkinsonism, so that continued benefit from chlorpromazine could be achieved or maintained. Related extrapyramidal manifestations are managed in the same way as parkinsonism and with equally good effect. Occasional patients with dysphagic symptoms should stop receiving the drug for long enough to recover, so that there will not be any danger from respiratory accidents associated with dysphagia.

Jaundice has been reported in a varying proportion of patients. We have seen 5 cases of jaundice in more than 1000 patients treated. In every instance, jaundice was of short duration, less than 10 days, and responded to the administration of fluids, withdrawal of the drug, and injection of ACTH in moderate doses for a few days. Studies of the liver function tests and liver biopsies indicate that jaundice is of the obstructive type and practically invariably benign. In 4 patients, use of chlorpromazine was reinstituted, without relapse of jaundice.

The complication that was a threatening experience when we first encountered it, but which has since become considerably less, is agranulocytosis. We have seen 4 cases, all of them women, in patients receiving chlorpromazine. One patient who had an associated lymphosarcoma died. The complexities of this case need not be discussed since chlorpromazine was not an exclusive factor in this patient's death. The other 3 cases of agranulocytosis that were purely the result of chlorpromazine administration recovered under treatment with adequate amounts of antibiotics and ACTH. This complication can be

adequately recognized if all patients who have fever or other evidence of infection, particularly with associated ulcerative or necrotic lesions, are immediately carefully examined for evidence of this complication.

CONCLUSIONS

In chlorpromazine (and other drugs), psychiatry has a weapon to combat psychotic illness at a more fundamental level, apparently changing the underlying pathologic physiologic process and allowing resumption of normal processes of adaptation. The relationships of the clinical effect of chlorpromazine and similar drugs to their pharmacologic effect on the midbrain and lower diencephalic centers have been previously noted, and further experience has been consistent with this thesis. Additional clinical and laboratory studies in this area will undoubtedly clarify and elaborate not only our understanding of the effects of drugs on psychoses but also our understanding of psychotic mechanisms in a physiologic setting.

Chlorpromazine is a potent means of treatment in both chronic and acute psychotic states. Psychotic states of both "functional" and "organic" types are benefited by drug treatment. Clinical procedures developed in drug treatment are indicated to help others feel more secure in the further development of this method. Drug treatment is not a substitute for re-education, rehabilitation, and psychotherapy, but it must be considered an important primary procedure before such efforts can be effective, since it is the underlying psychotic process that seems to be relieved by drug treatment.

RESUMEN

Con la clorpromazina—y otras drogas—, la Psiquiatría cuenta con un arma para combatir la psicosis a un nivel más fundamental, cambiando al parecer el proceso fisiopatológico subyacente y permitiendo la reanudación de proceso normal de adaptación. Se ha observado la correlación del efecto clínico de la clorpromazina y drogas similares con su efecto farmacológico sobre el mesencéfalo y los centros diencefálicos inferiores, y las experiencias posteriores han confirmado esta tesis. Los futuros estudios clínicos y de laboratorio aclararán sin duda alguna y desarrollarán no sólo nuestros conocimientos sobre los efectos de las drogas en la psicosis, sino también nuestra comprensión de los mecanismos psicóticos en un cuadro fisiológico. La clorpromazina es un poderoso medio de tratamiento tanto de los estados psicóticos crónicos como de los agudos. Los estados psicóticos de tipo "funcional" y "orgánico" se benefician por el efecto de esta droga. Los procedimientos clínicos desarrollados en el tratamiento con este medicamento indican que ayuda a otros a sentirse más seguros en cuanto al desarrollo ulterior de este método. El tratamiento con esta droga no es un sustituto de la reeducación, rehabilitación y psicoterapia, sino que debe considerarse como un importante procedimiento primario antes que tales esfuerzos puedan ser eficaces, ya que el proceso psicótico subyacente parece aliviarse con el uso de esta droga.

RESUME

La chlorpromazine (et d'autres drogues), permet à la psychiâtrie de mener le combat contre les maladies de psychose sur un niveau plus fondamental, et de changer ostensiblement

le processus physio-pathologique de base, ainsi rendant possible une reprise des opérations normales d'adaptation. On a déjà noté les rapports entre les effets cliniques de la chlorpromazine et de drogues similaires, et leur effet pharmacologique sur le mésencéphale et les centres diencéphaliques inférieurs. Des expériences supplémentaires s'accordent avec cette thèse. De nouvelles recherches cliniques et de laboratoire dans ce domaine eclairciront non seulement les effets des drogues sur les psychoses, mais elles nous instruiront aussi sur les mécanismes des psychoses dans un cadre physiologique.

La chlorpromazine est un traitement efficace dans les états chroniques de psychose aussi bien que dans les conditions aiguës. Les états de psychose tant fonctionnels qu'organiques se trouvent améliorés du traitement par les drogues. Les procédés cliniques, élaborés au cours de ce traitement, sont indiqués pour donner à d'autres plus d'assurance dans leur developpement subséquent de cette méthode. Le traitement par les drogues ne remplace pas la rééducation, la rehabilitation et la psychothérapie. Mais il faut le considerer comme un procédé primaire important qui prepare le terrain pour la réussite de pareilles démarches, étant donné que c'est le processus de fond qui semble être soulagé par les drogues.

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"Ambulatory" Treatment with Chlorpromazine

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It is generally admitted that although chlorpromazine is of the greatest therapeutic interest in neuropsychiatry, it cannot be used without respecting a certain number of precise rules that sometimes limit its applications. These rules include strict surveillance, whether in a hospital or in a private clinic; more or less absolute maintenance of the patient in the supine position; control of arterial tension, body fluid constants, and exchanges; and preference for parenteral administration and a relatively high dosage plan.

Our experience with chlorpromazine, now nearly four years old, showed us that this "major therapy" was not all that could be obtained with this drug; that by prescribing it in this manner the benefit of the treatment was withheld from a number of patients with minor psychic disturbances or with various neurologic syndromes who should not and could not be submitted to such extensive and rigorous rules. For these patients, we developed an "ambulatory" treatment that will be described. The results have been interesting, the use of the drug is relatively simple, and the risks are practically nil. This ambulatory treatment is useful in treating neuroses and psychoneuroses, renders great service in certain neurologic disturbances, and can bring relief, hitherto impossible, in certain serious chronic psychoses such as the hallucinatory and interpretative types. Despite all the interest that this method holds, it must be noted that it is not as widespread as it should be. We believe that a study of the general results obtained in 150 patients suffering from a variety of affections will overcome the apprehensions of those, too great in number, who consider chlorpromazine a compound with remarkable action but requiring very delicate handling.

The ambulatory treatment plan does not, of course, produce constant results, and it does not pretend to be self-sufficient; but it has great advantages and is sometimes irreplaceable. It can be directly instituted and maintained throughout; sometimes it is found insufficient and must be replaced with "major therapy." Often it is used to complement radical treatment, prolonging its effect for weeks or months, thus maintaining the value of the initial treatment. The advantage of this treatment is that it can be instituted for an unlimited time with practically no danger, even after prolonged therapy. We will have occasion to mention 1 patient among others, who received this treatment more or less continuously since 1951.

METHODOLOGY

Certain rules must be followed if the treatment is to be effective and without inconvenience. By definition, ambulatory treatment is for nonhospitalized patients who continue to live in their family surroundings, some even continuing in their work. They must be seen at varying intervals in order to regulate dosages. A certain number of urban patients are included in this study.

Clinical Material. Our 150 subjects are grouped as follows: neuropathic depression, 34; obsessional and phobic neurosis, 30; psychoneurotic and psychotic depression, 23; chronic systematized delirium, 10; postcommotional syndrome, 11; neurologic pain, 30; and miscellaneous, 12.

In order to avoid error in the classification of our cases, some explanation is required. Under the term "obsessional and phobic neuroses," following the most frequently given symptomatic description, we grouped disorders consisting essentially of obsession, obsession-compulsion, and various phobias that are associated more or less with frequent crises of anguish. Whether these manifestations are a few months or a few years old, examination nearly always discloses a deep and old residue of various disorders corresponding to the psychasthenia of Pierre Janet. We are concerned here solely with pure neurotic structures, exclusive of psychoneurotic anxieties. Under the term "neuropathic depression," we have gathered manifestations that are polymorphous in their most apparent clinical expression but homogeneous in the fundamental structure that they implicate. Symptomatologically, there is a common core of physical and psychic asthenia, sadness, or anxiety, to which are added the following disorders varying in duration: irritability (from the simplest irritation to violence against the person); visceral, proprioceptive, and sensorial sensations of great variety; and neuropathic attacks ranging from a crisis of weeping to falling and convulsions. The polymorphism of this group is also found in the development of manifestations presented by certain patients in the course of a more or less protracted evolution. To some of them one might apply the term "psychosomatic." Between this group and that of the obsessional neuroses, there are few transitional forms; for this reason the two groups must be clearly distinguished.

In order to preserve the homogeneity of this group, we did not include cases in which, in the course of evolution, the depression took on overtones of melancholia, thus justifying the qualification of psychoneurotic in the modern sense. These were grouped with authentic cases of melancholia derived partly from manic-depressive states and partly from presenile or senile involution with other cases of undetermined origin.

The field of chronic systematized deliriums is quite classic. Four of our cases are chronic hallucinatory psychoses, 3 are delirium of interpretation, 3 others comprise a delirium induced in a debilitated case, 1 is a puerperal psychosis and an interpretative delirium imposed on melancholic hyperthymia. Postcommotional syndromes include neuropsychiatric disorders with any sign of precise localization, appearing as a result of violent cranial trauma. As for the "neurologic pain," these comprise a variety of pains rebellious to treatment, in particular zonal algias.

Routes of Administration. Ambulatory treatment is generally instituted with tablets of 0.025 Gm. Sometimes the 4 per cent solution is preferred, as this permits delicate fractionation, 1 drop corresponding to 1 mg. Besides the oral route, it is possible to use the rectal route, either exclusively (exceptional) or concurrently. There are suppositories containing 0.1 Gm. and 0.025 Gm.; and it is not exceptional to prescribe a suppository of 0.1 Gm. at night, although some patients do not tolerate rectal administration well, while others accept it willingly. As for the parenteral route, this is used only very exceptionally

in our method. (It must be emphasized that it is not prudent to prescribe intramuscular injections of chlorpromazine for patients who are not under strict control.) In some cases, a short period of hospitalization has preceded the ambulatory regimen, and in such cases the intramuscular route remains valuable.

Dosage and Administration. As with most drugs that act on the central nervous or vegetative systems, one must determine the optimum dose for each patient. Tolerance to the drug and the success of the treatment depend on how the dosages are established. It is essential that dosage should be progressive, and that it be administered in divided doses at determined intervals during the day. In this way, one avoids the initial administration of too high a dose that might provoke saturation phenomena, such as somnolence, and risk accidents of orthostatic hypotension in patients who are not in decubitus. The nature of such accidents will be studied later.

If chlorpromazine is administered initially in small doses, in a minimum of five divided doses, and if the increase in daily doses is progressive, no accident is to be feared, and neither rest nor the supine position are necessary. In subjects who are initially hypotensive, this rule must be strictly enforced. In such cases, it is perhaps prudent to advise patients to remain lying down for a half-hour following a dose of the drug; and they must particularly be given neither a high dose to start with nor a few divided doses. Naturally, it is necessary to warn the patient and his family of the possibility of such incidents, which generally carry small risk, but which must be combatted immediately by placing the patient in a supine position, even with the head lower than the body.

We advise the administration of five divided doses at approximately equal intervals. A stronger dose must not be given on awakening, and the five doses should be more or less equal. The hours we advise our patients to take the drug are on awakening, at 10:30 a.m., 1:00 p.m., 5:00 p.m., and 8:00 p.m. Sometimes we add a dose on retiring, a dose that can be stronger, since all the incidents inherent in administering chlorpromazine, somnolence or lipothymia, produce no inconvenience during the night.

In practice, we begin the first two days with a daily dose of two and a half tablets of 0.025 Gm. each; each of the five doses therefore consists of a half tablet. The increase in dosage must be slow and progressive. Every two days we add a half tablet of 0.025 Gm.; the patient thus replaces a half tablet with a whole one every two days, arriving progressively at a dose of five tablets a day. A halt in this progression will be determined by "feel," and is based on two factors: (1) the improvement in the patient and the appearance of relaxation, and (2) the advent of diurnal somnolence. In this way, the patient himself arrives at his own individual dosage, which is variable. It can be lower than the recommended dose of five tablets daily, i.e., 0.125 Gm., or it is sometimes higher, in which case doses are increased from one and a half tablets to two. In general, in ambulatory treatment, the dose of five tablets a day, or 0.125 Gm., seems to be the average dose, but there is no absolute rule. Some patients take doses of 0.2 Gm. and even 0.3 Gm. without feeling the slightest malaise, and with good results. The good effect obtained and the patient's toleration are the best guides.

In cases where it is felt that ambulatory treatment should be more rapid and the required

dosage achieved before 10 days, either because the patient is suffering or because his psychic state demands a more rapidly effective therapy, one should begin with stronger doses, starting from the first day with a daily dose of 0.125 Gm. In such cases it is prudent to advise the patient to remain at rest for one hour following each dose and to reduce the dosage if there is any intolerance. As will be seen later, the risk of malaise or lipothymia exists only for a short time. After 8 or 10 days it is unnecessary to take the same initial precautions; and some of our patients manage to absorb from 0.05 to 0.075 Gm. in one dose without disturbances of any kind.

In cases where a rapid result is desired, the rectal route may be used for four or five days. We administer a suppository of 0.1 Gm. of chlorpromazine morning, noon, and night, with more or less complete rest. Equivalents in activity are approximately 0.05 Gm. oral to 0.1 Gm. rectal or 0.025 Gm. intramuscular.

Management of Patient. Patients undergoing ambulatory treatment must be carefully watched. When a patient has been hospitalized, we have him return at the end of the first week, then eight days later, and at longer intervals thereafter. Naturally, the patient is warned of the possible risks of the treatment, and he has the duty to reduce his dosage, to return for consultation, or to telephone the physician if any incidents occur. By respecting these rules, we have never had any serious accident. Some less docile patients may divide their dosage into three, finding this more convenient, and they might suffer nothing thereby, but they must be told of the risk of ingesting massive doses at fewer intervals.

Length of Treatment. In general, ambulatory treatment is quite prolonged, and it must be maintained as long as the patient feels the need for therapy. The length of treatment, as with dosage, depends on the dysfunction under treatment. Whereas some subacute affections are rapidly improved, other chronic states require lengthy, even indefinite treatment, as is the case in certain chronic psychoses. When we study the various illnesses treated, we shall examine indications for dosage and length of treatment. At this point we will only note that in cases subjected to prolonged treatment, clinical surveillance must be complemented by biologic surveillance, comprising regular control of arterial tension, study of the renal and hepatic functions, and periodic examination of the blood picture, especially the leukocytes. Such precautions are useful, although in practice these tests are not indispensable.

When treatment is prolonged, it is unnecessary to maintain the initial dosage. Improvement generally occurs as soon as the optimum dosage is in force. This must then be maintained for 8, 10, or 15 days, after which it can be gradually diminished. Where the illness evolves favorably, the reduction of dosage should be slowly progressive, maintaining small doses for a certain time before total discontinuance.

The lack of success or failure indicate if treatment should be interrupted. Sometimes it is necessary to replace ambulatory treatment with hospitalized "major therapy." In such cases, parenteral administration of stronger doses of chlorpromazine, eventually associated with the barbiturates, obtains the results that the ambulatory regimen was unable to produce. Parenteral use of the drug is usually indicated for short treatments; ultimately ambulatory treatment is restored to its rights and helps to complete therapy. In other cases,

one is obliged to abandon chlorpromazine, either because it is unable to improve the patient or because intolerance makes it contraindicated.

Combined Therapy. For best results with ambulatory treatment, it is sometimes necessary to combine other drugs with chlorpromazine. The combined use of small doses of barbiturates sometimes reinforces sedation; phenobarbital, amobarbital, or brophebarbital can be used. Very small doses are effective where larger doses would be badly tolerated and could cause somnolence. In the evening, to obtain normal sleep a stronger hypnotic such as butobarbital, mebubarbital, or amobarbital may be used. To combat somnolence sometimes induced by chlorpromazine, one can have recourse to caffeine or simply coffee, or to small doses of amphetamine, which stimulate but do not excite. Adjuvant use of preparations of phosphorus, magnesium, or glutamate are frequently of use. Against palpitations, physostigmine is sometimes useful, as is an injection of calcium gluconate. Naturally, numerous other combinations are possible according to the case, and there is also no difficulty in adding hormones and vitamins to the chlorpromazine therapy. We might note that in the majority of cases ambulatory treatment is with chlorpromazine alone and, therefore, adjuvant therapy does not affect the treatment as a whole.

COMPLICATIONS

Some incidents can disrupt ambulatory treatment with chlorpromazine. These are generally benign and disappear either spontaneously or after modification of the regimen; seldom are they sufficiently important to interrupt treatment.

No factors permit one to foresee the possibility of these incidents. Neither age, sex, nor the type of ailment treated play any part. Dosages leading to intolerance vary from one patient to another, although they remain fairly constant for any individual. Some particularly sensitive subjects may be afflicted with somnolence on only one-half tablet, whereas others tolerate a dose of two or even three tablets.

Minor Incidents. These may include nervous, digestive, cardiovascular, and, occasionally, cutaneous reactions. At the beginning of treatment, it is usual to see the apparition of somnolence if the dose is too high. All degrees are seen, from a simple transitory drowsiness giving the impression of a light mist before the eyes, to a more profound obnubilation that renders work impossible and tends toward sleep. A reduction of dosages generally causes these disturbances to disappear, or caffeine or other stimulants can be prescribed. Frequently the patient develops a certain mental slowness, with indifference toward his habitual worries, which is a fairly beneficial phenomenon. It should be noted that the ingestion of alcoholic liquids during ambulatory treatment with chlorpromazine provokes such manifestations. Dryness of the mouth is sometimes seen, but this inconvenience is minimal and is not an important obstacle. Some patients complain of heartburn, which can easily be avoided by administering the tablet with either sugared water or some food; actually this symptom is a burning sensation in the lower esophagus occurring when the patient omits the precaution of taking the drug with sufficient liquid. Constipation is a frequent complication, but this can easily be combatted with a laxative. One should also note the possibility of rectal intolerance to suppositories, which is relatively rare and usually

seen only after a few days. Palpitations and tachycardia are occasionally encountered, sometimes only during the first few days of therapy but sometimes for longer periods. These manifestations are incidents of minor orthostatic hypotension that can be treated with sedatives associated with physostigmine or calcium injections. Sometimes manifestations are sufficiently severe to interrupt treatment. Dermatologic accidents are absolutely exceptional, whether as eczema, drug allergy, or erythema due to photosensitization.

Major Incidents. These are in the nervous and cardiovascular field, and are rarely systemic. Major nervous incidents are exceptional. They include paresthesias of the lower extremities, usually seen in the evening and accompanied by feelings of impatience, and painful tension of muscles in the lower limbs. Less frequently, irregular and infrequent muscular spasms that remind one of myoclonia may occur. Nervousness and excitation are sometimes observed, a phenomenon resulting commonly from the use of phenothiazines. Some subjects react with irritability, insomnia, excitation, and anguish. Such incidents are absolutely exceptional, but when they occur they require the immediate interruption of therapy and the further abstention from any of the phenothiazines. The appearance of extrapyramidal signs or of the pseudoparkinsonian syndrome are never seen during ambulatory treatment, when only moderate or low doses of chlorpromazine are used, although they have been seen in treatments with higher dosages. On three occasions we asked ourselves whether chlorpromazine was responsible for incidents of that kind, but after inquiry it was found that the manifestations preceded the treatment and had escaped initial examination. In one case, a moderately intense trembling was seen in a female patient during treatment for a depressive state; however, her family revealed that this trembling had existed before treatment. The intravenous injection of 0.025 Gm. of chlorpromazine brought about the total disappearance of the trembling. In the case of an elderly woman who was receiving small doses of chlorpromazine, amimia and slowness of gestures were noticed; and the involuted melancholia in this pseudobulbar subject was not modified with suspension of treatment. In this regard, it is interesting to note that on several occasions we administered chlorpromazine to patients with authentic Parkinson's disease, and we frequently observed a remission in symptoms. In one particular case we were able to obtain a remission of oculogyric crises that had been intractable until then.

The major vascular accidents, which frequently instill a fear of using chlorpromazine, are manifestations of orthostatic hypotension that provoke lipothymia and even more prolonged syncopes. These manifestations are practically never seen if one respects the rule of slow and progressive dosages. Moreover, they need not be feared if treatment has lasted more than a week, even at fairly high dosage. The few rare cases of such incidents in our patients were due to an error in dosage, the patient having started off with a high initial dose. In general, such incidents are not serious if a horizontal position is immediately instituted, but if the subject keeps his head up while lying down, or if he remains a long time without lying down, complications can become serious. One must be particularly prudent with hypotensive patients in whom the simultaneous administration of epinephrine, ephedrine, or any other analeptic will avoid such disturbances. We must emphasize, however, the scarcity of risks incurred in ambulatory treatment if these rules are strictly applied.

Systemic toxic manifestations may appear in patients subjected to prolonged treatment. It is prudent, in dealing with patients who are receiving chlorpromazine for several months or more, to submit them to hematologic control and to test renal and hepatic function. One practically never sees blood dyscrasias; although, in one of our patients agranulocytosis set in with a fatal outcome. However, this was an elderly man who had been taking very small quantities of chlorpromazine, and other drugs, for a long time. The role of chlorpromazine is, therefore, very debatable in this case. Renal disorders are never seen. As for hepatic disorders very frequently reported in the Anglo-Saxon countries, we have observed them only exceptionally. In our series of patients treated with chlorpromazine, which is very much larger than the one reported in this paper for ambulatory treatment, we observed only 1 case of retention icterus. This condition lasted 15 days, during which time chlorpromazine was suspended, but it was possible to reinstate the drug and to maintain it for several months without any recurrence of the icterus and without any alteration in hepatic function.

One last factor should be emphasized: even in the longest durations of therapy we have never observed the slightest sign of toxicomania. In prolonged treatments, the subjects generally tend to reduce their dosages; there is no addiction and no withdrawal symptoms. We have never seen a patient continue to take the drug against our indication.

RESULTS

Good results are those that permit both the return to a normal family and social life and the disappearance of the more painful subjective disorders. Mediocre results indicate noteworthy improvement but only permit a partial return to activity, as for example housewifery. Behavior that is not improved, even if subjective disorders are partially relieved, is considered as failure.

In 34 patients with neuropathic depression, we had 3 failures that were partly due to an intolerance to chlorpromazine and partly to our inability to achieve an effective dosage level. Results were good in nearly half the cases (16 of 34). Cures appear to be obtained more easily in young adults than in middle-aged persons. Length of treatment was less than a month in 16 patients, from one to three months in 15 patients, and more than three months in the others. Good results were obtained with a daily average dose of 100 mg. In 2 patients considered as failures, the renewal of chlorpromazine medication in hospital produced a cure. The following are 2 cases in which we achieved good results:

Mrs. M., 38 years old, was nervous, anxious, sad, and incapable of working. She presented palpitations, choking, colonic pain with spasm, and frequent weeping. The disorders were particularly acute in the last year and had resisted all usual treatment. A dosage of 100 mg. a day for a month caused the disappearance of the disorders, the renewal of normal activity, and an increase in weight, contrasting with a loss of 15 pounds in a previous year.

Mrs. T., 35 years old, was asthenic, anxious, discouraged, nervous, wept frequently, and shouted whenever thwarted. Therapy with 100 mg. daily produced, at the end of nine days, the disappearance of crises and an improvement in the hyperemotional structure. One month later all these disorders had vanished.

In the treatment of obsessional and phobic disorders, results were good in two-thirds of

the patients. Three failures were caused by the inability to administer the required dosage. In 8 patients, treatment lasted less than a month; in 11, it lasted between one and three months; in 6, it was between three months and a year; and 5 were treated for more than one year. In 1 case in which failure occurred despite a well-ordered ambulatory regimen involving the administration of 200 mg. daily for three weeks, subsequent hospitalization succeeded very well. The average dose used in ambulatory treatment was 125 mg. daily. The following examples illustrate 1 case in which good results were achieved with low dosage over a short period, the other of more prolonged therapy:

Mrs. F., 28 years old, was psychasthenic all her life. Since the preceding year, she presented a permanent anxiety with agoraphobia and an obsessive fear of killing her child; her inactivity and apragmatism were total. She had previously received five electroshock treatments, as well as numerous forms of sedation without result. The administration of 50 mg. of chlorpromazine daily for three weeks was sufficient to eliminate the anxiety and the behavior disorders.

Mr. M. B., 60 years old, was psychasthenic for many years, and presented a depressive state with total inactivity and a few suicidal tendencies. He was permanently obsessed with the idea of entering his neighbors' homes and seeing himself writing at their tables.

He started on 100 mg. daily, but by the end of a month he was on a daily dosage of 250 mg., which was well tolerated. Excellent results (euphoria and renewed occupation despite the persistence of a few anxieties) permitted the dose to be reduced to 100 mg. daily, which was maintained for a year. Excellent results were maintained. Fourteen months after instituting therapy, various blood and renal tests gave normal results.

These two examples illustrate the action of ambulatory treatment in patients with obsessional and phobic disorders. It should be noted that sedation of the anxieties is usually complete, although some obsessions may persist. These the patients regard with indifference, and they usually do not interfere with a resumption of activity.

Of the 23 patients with psychoneurotic and psychotic depression, we obtained 15 good results. Failure of treatment was noted in 2 patients. In 11, treatment lasted less than one month; in 8, it was between one and three months; in 3, between three months and a year; and in 1, more than one year. The good results were obtained with a daily average dose of 100 mg.; in 5 patients, treatment was begun in a hospital for a week. One failure was later eliminated by hospitalization. The following is a brief report of a case:

Mrs. M. L., 60 years old, was in a depressive state of several years' duration but without previous periodicity. This culminated in an anxious melancholia with apragmatism, prostration, and a few cenesthesias such as the sensation of "a pebble in the head that prevents thinking." She received five electroshock treatments that brought a very transitory improvement; a subsequent course of 12 electroshock treatments with curarization obtained no results. She was placed on 75 mg. of chlorpromazine daily; by the end of the first week activity was resumed, and rapid improvement followed. This patient was followed-up for 10 months. As long as she remained on chlorpromazine her behavior was normal. She complained only of a few cenesthesias that did not, however, disturb her normal life. On cessation of treatment there was a relapse. The patient was lost sight of after a year.

We treated 10 patients with chronic systematized delirium during a fairly long period in order to permit drawing valid conclusions on the basis of observation. One patient has been treated for nearly four years; 2 other more recent cases are not included, as treatment was followed for only a few weeks. The result of treatment in these generally severe and

chronic affections, in which the prognosis is serious, is usually quite good. For this reason we consider this group as a specimen indication for ambulatory treatment, inasmuch as these are chronically ill patients who without treatment might become serious mental cases requiring segregation; chlorpromazine clearly suspends some of the more sensational and disturbing manifestations in their psychic state. As the action of the drug is only suspensive, prolonged treatment is required. This is as valuable as, for example, the symptomatic treatment of an epileptic, as it suspends the antisocial reactions of the patients and assures them an almost normal life.

The 10 patients who were followed for several months included 3 with classic chronic hallucinatory psychosis; 1 with chronic postencephalitic hallucinatory psychosis; 1 with chronic delirium of interpretation; 2 with senile delirium; 1 with delirium ideas in late puerperal psychosis; 1 with delirium ideas in an atypical depressive state; and 1 with delirium, induced in the husband of one of the foregoing patients suffering from chronic hallucinatory psychosis.

Chlorpromazine exercised a constantly effective and complete action on the psychic and even psychomotor excitation, as well as on the anxiety factor that is common to all these deliriums. What is even more interesting is the suspensive action of the drug, in some cases curative, where the delirium reactions were of the aggressive or querulous type, as well as on the delirium factor itself. In general, the interpretative or hallucinatory mechanism appears to vanish or at least to remain in suspense. In the 4 patients with chronic hallucinatory psychosis, the hallucinations were stilled under treatment, and in 1 patient this action appeared to persist several months after stopping treatment. In general, the suppression of active delirium seemed proportional to the intensity of dosage, but after a certain period of treatment this relationship with the anterior delirium was less clearly associated with the adjuvant psychotherapy. During treatment, results were always excellent as regards mood and behavior of patients; antisocial acts (family disputes, quarrels with neighbors, complaints to the authorities) disappeared, permitting a renewal of domestic and even professional duties.

Apart from the 1 patient in whom the psychosis was completely erased, permitting the suspension of all treatment after several months, the general effect was only suspensive, and the delirium tended to return when dosage was reduced or stopped. It is, therefore, important to explain to the patient's family the necessity of maintaining a continuous therapy with chlorpromazine. This is difficult to do, as in the absence of any consciousness of the disorder, subjects find it difficult to submit to a therapy of which they understand neither the object nor the value.

Loading doses vary between 125 and 300 mg. daily, but subsequently dosage can be reduced to 50 or 100 mg. One should administer the optimum dose, based on results obtained, sufficient to calm the delirium of interpretation and permit normal activity. In some cases we attempted to press treatment with chlorpromazine to its maximum, and we were able to arrive at doses of 325 mg. daily. This resulted in a suspension of all delirium phenomena, the patients themselves recognizing that they were free of all auditory or cenesthesic hallucination. When dosage was reduced, some delirium of interpretation re-

turned, but the patients did not complain or speak of it spontaneously; it was necessary to question them to discover that the disorders continued. Moreover, all secondary reactions to interpretation or hallucination disappeared.

This treatment makes it possible to avoid an internment that would sometimes appear necessary, and it is possible that the continuation of ambulatory treatment could facilitate the dismissal of a certain number of chronic delirium patients now interned, naturally under surveillance.

Of the 11 patients with postcommotional syndrome, we distinguished 8 where there was only a subjective syndrome characterized by cephalgia, vertigo, disequilibrium, ocular dysfunctions, tinnitus, and various mnemic disorders. Five successes were rapidly obtained after about 15 days of treatment with chlorpromazine; another patient was unable to tolerate the increase in dosage; in another patient where ambulatory treatment failed, a very good result was obtained later with treatment by the parenteral route. The other 3 patients with postcommotional syndrome comprised associated manifestations: in 1 patient suffering from a serious reaction depression following the death of his wife in an accident, there was an excellent result; in another patient there was an associated sinistrosis and the result was mediocre; in the last patient, in whom cephalgia was linked with chronic otitis, the result was also mediocre.

In the 30 patients with neurologic algias, we had 7 with postzoster pain, 3 with post-traumatic neuritis migrans, 2 with painful paresthesia of the lower limbs, 2 with cephalic vascular pain, 2 with thalamic syndrome, 3 with facial pain, 1 with glossopharyngeal neuralgia, 2 with brachial neuralgia, 1 with dorsal neuralgia, 1 with neuritis pudendalis, and the remainder comprising hemicranias or cephalgias of varying intensities.

In order to evaluate the results, we took careful account of the total behavior of the patient, attempting to evaluate the quality of his sleep, the more or less anxious aspect of the facies, and the ability to undertake effective professional activity.

Postzoster pain is frequently improved with chlorpromazine, but if the condition is an old and rebellious one, high dosages are required. Acute conditions must not be treated on an ambulatory basis, but should receive high dosages of chlorpromazine parenterally. In the 7 patients in whom we instituted ambulatory treatment, 6 gave good results and 1 was a medium success. The latter was a man of 82 years with postzoster pain of three years' standing, and despite the continuation of the pain, his behavior was improved. We do not include the results obtained with parenteral treatment in the particularly severe cases of postzoster pain, where the percentage of improvement was lower than in the average forms of the condition described above, although these results are still of interest.

The 3 patients with post-traumatic neuritis migrans reacted very well. In about 20 days, patients were able to resume work, although they had for some time suffered acute pain and insomnia.

Ambulatory treatment with chlorpromazine gave good results in 2 patients with paresthesia of the lower limbs and in 2 patients with cephalic vascular pain. On the other hand, in 2 patients with thalamic syndrome, results were mediocre. The true trigeminal neuralgia is only rarely influenced by ambulatory treatment; results have sometimes been obtained

with parenteral treatment, but these are not mentioned here. On the other hand, we obtained fairly good results in cervicobrachial neuralgia, in neuritis pudendalis, and in certain refractive cephalgias of which 2 were linked with Paget's disease and 1 with an internal frontal hyperostosis.

We noted several disparate results in ambulatory treatment with chlorpromazine: failure in 3 patients with labyrinthine vertigo; mediocre results in 2 with tic; improvement of oculogyric crises in a parkinsonian female patient; improvement in a dipsomaniac presenting several bouts a week; and improvement in an unbalanced individual who had been intoxicated with carbon disulfide. Moreover, we obtained no results in patients with gout, but good results in 3 with vesical pain.

DISCUSSION AND CONCLUSION

Before presenting our conclusions on the place reserved for ambulatory treatment with chlorpromazine in neuropsychiatric therapy, several questions should be posed. In which patients is it indicated? Should it be instituted at once or only after parenteral treatment? Does its failure foreshadow the failure of more intensive treatment? How long should treatment last? Does it comport any risks? What are its advantages?

Ambulatory treatment with chlorpromazine is recommended in all cases analogous to those we have described. Treatment should be instituted systematically in all "mildly mental" patients, i.e., all neuropaths, depressives, psychasthenics, obsessive and phobic neuroses, and psychoneurotic depressives. There is an absolute indication in the group of chronic hallucinatory and interpretative psychoses; in spite of the usually severe prognosis, such cases can be considerably improved on condition that dosage is sufficiently high and that treatment is prolonged. As the drug's effect is only suspensive, it is exceptional to obtain a cure of the psychosis and to suppress the delirium of interpretation. Ambulatory treatment should also be tried in the presence of any postcommotional syndrome, in all chronic and refractive pain, in cephalgias, and in neuritis migrans.

It can also be instituted in more serious psychiatric syndromes, as we used the treatment in true and severe melancholic states.

There is one evident contraindication: when the patient's excitation can make him dangerous, or when there are clear ideas of suicide and his family cannot exercise the necessary surveillance. Further, when it is considered indispensable to associate treatment with complete rest, it is useless to have recourse to ambulatory treatment. Sometimes the beginning of treatment by the parenteral route precedes the discharge of the patient, after which he can continue therapy. Ambulatory treatment should be avoided if arterial tension is low, if the subject is emotional, or if one considers that therapy should be closely controlled. Consequently, this method can be applied in a wide field subject to a certain critical approach to indications, refusing to treat all serious mental cases apart from the chronic interpretative and hallucinatory psychoses.

Ambulatory treatment can be instituted immediately or after one or two weeks of controlled hospital therapy, whichever is more convenient. This system is recommended to

physicians who have no extensive experience with chlorpromazine and who wish to observe initial reactions. These variations in detail have nothing to do with general indications.

The failure of ambulatory treatment because the patient cannot tolerate dosages, or has not followed the rules of progressive dosage indicated, or suffers from some malaise should not prejudge the effect of general treatment by the parenteral route. In several cases we were able to obtain good results where previously we had noted failure.

Ambulatory treatment can be maintained a long time, though it is not indispensable to make it indefinite, depending on the condition of the patient. It is evident that, when the depressive state has disappeared, the cenesthesias have been erased, and the state of irritability has been changed, it is unnecessary to continue treatment. A recommended course is to diminish treatment gradually, maintaining the patient on small doses of 25 mg. daily, in two or four divided doses. On the other hand, in the treatment of certain chronic conditions, therapy should be indefinite as long as no other form of therapy brings better results. Interpretative and hallucinatory psychoses illustrate this, as for example, the female patient treated for nearly 4 years and who is now able to maintain a normal social life because of chlorpromazine.

The dangers of ambulatory treatment are minimal and are reduced almost to zero if the precautions we have described are respected.

There are important advantages in the ambulatory treatment plan that it is practically unnecessary to emphasize. Its great advantage is that it frees the patient from the depressing atmosphere of a hospital or a clinic. For certain patients suffering from the less severe psychic disorders, which make them "mildly mental," or for patients with certain algias, it is unnecessary to impose complete rest; in fact, in some of these milder cases, the continuation of social activity contributes to the success of the treatment. It is thus possible to obtain a really progressive rehabilitation while maintaining at least partial activity. The ability to prolong an indispensable form of therapy for weeks, months, or even years is a weighty argument in favor of ambulatory treatment. In connection with some of our observations, we were able to conceive of chlorpromazine as being the "insulin of the nervous."

In conclusion, we can affirm that there is no inconvenience in trying the application of chlorpromazine in ambulatory treatment, that there is no danger if the rules of administration are respected, that the results obtained are frequently most valuable, and that, wherever indicated, this method should be used, as it is simple to institute and its value is self-evident.

SUMMARY

The authors present results in 150 patients with psychiatric and neurologic disorders treated on an ambulatory basis with chlorpromazine. They describe the technique of this method, which comprises no difficulties if the rules are observed, beginning with low doses, progressive increase of doses, and oral administration during more or less prolonged periods, with periodic control of the patient, who is himself instructed in how to deal with possible incidents. This method, which permits patients to continue a certain professional activity

and to avoid hospitalization or admission into a psychiatric service or clinic, is particularly valuable in the treatment of neurotic or psychotic depressive states, of chronic hallucinatory and interpretative deliriums, of postcommotional syndromes, and of various algias. The percentage of favorable results obtained is a high one; even in cases of initial failure, other forms of therapy can be instituted.

This method of treatment is particularly recommended for the "mild mental" patients, in cases of chronic delirious psychosis, in the postcommotional syndromes, and against refractive pain.

RESUMEN

Se obtuvieron buenos resultados en cierto número de pacientes tratados con clorpromazina sobre base ambulatoria. En una serie así tratada de 150 casos de trastornos psiquiátricos y neurológicos, se registró un alto porcentaje de resultados favorables. El tratamiento básico consiste en su institución a dosis bajas, empleando la administración oral por períodos de tiempo más o menos prolongados, e instruyendo al paciente sobre cómo debe hacer frente a los posibles incidentes que puedan presentarse. Se observó que este método de tratamiento es de valor en los estados neuróticos y en las psicosis depresivas; en los deliros de alucinación crónica, en los estados post-conmocionales y en varias algias. También se obtienen beneficios psiquiátricos al libertarse a los pacientes de la atmósfera de hospital y poder mantenerlos en un ambiente más o menos normal.

RESUME

De bons résultats ont été obtenu chez un nombre de malades traités avec la chlorpromazine par cure ambulatoire. Les auteurs rapportent un haut pourcentage de bons résultats dans une série de 150 malades atteints d'affections psychiatriques et neurologiques. Le traitement débute par des doses faibles par voie buccale pendant une durée plus ou moins prolongée, en informant le malade lui-même des incidents possibles et du moyen d'y parer. Cette méthode est surtout intéressante dans le traitement d'état dépressif névrotique ou psychotique, de délire chronique hallucinatoire, de syndrome post-commotionnel et d'algies diverses. Un avantage du point vue psychiâtrique est d'éviter aux malades l'atmosphère d'hôpital et de les maintenir dans un environement plus ou moins normal.

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Incidents and Accidents in Chlorpromazine Therapy

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The successful therapeutic effects obtained with chlorpromazine pose the problem of possible incidents and accidents. The activity of the drug in hospitalized patients in a state of agitation led to its being called "a new Pinel." As was the case with the liberation of the mentally deranged, the new freedom with respect to morbid impulses, gained through the use of the drug, created new problems that up to now have not received much attention. What use will the personality make of the newly developed situation? How will the patient receive the drop of his inner impulses? Certain hypomaniacs and other patients treated with average doses of chlorpromazine do not immediately accept the inner serenity produced by the drug and fight it, thereby developing a secondary excitation. In labile neurotics and insecure individuals, the experience of hypotension or of a simple decrease in activity may be felt as a new threat to the ego, which is shaken by anxiety, to the detriment of the beneficial therapeutic effects. Both these conditions, which throughout this paper will be considered as psychologic incidents, indicate the combined use of psychotherapy so as to integrate the drug's activity with the psychologic effects on the over-all personality; it is what the senior author calls "convergent psychosomatic therapy."

The accidents and incidents associated with the use of chlorpromazine must be considered in this perspective. We, therefore, differentiate between the incidents and accidents resulting directly from the somatic activity of the drug and those that are caused by disturbance of the psychosomatic integration of the somatic effects.

SOMATIC INCIDENTS AND ACCIDENTS

Jaundice. Several authors have described temporary jaundice syndromes without having been able, however, to establish a clear link with the possible toxic effects of chlorpromazine. Here in Lisbon we observed the case of an asthenic female patient who previously presented clinical signs of hepatic insufficiency. The patient became ill with jaundice, severe pain, and nausea on the fifth day of sleep therapy with chlorpromazine combined with sodium amytal. She was cured after the suspension of treatment, with the changes in the Hanger and Takata-Ara reactions persisting. In some of the cases reported in the literature, there were no clear laboratory signs of hepatic changes; others presented changes, although of low intensity, such as that of the glutathione content in the blood,[9] slight changes in the cephalin-cholesterol reactions in 50 per cent of the cases, and changes in the protein serum values and the albumin-globulin coefficient in 30 per cent of the patients;[12, 13] and in some patients there was an increase in serum bilirubin and alkaline phosphatase values.

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It is interesting to note that when the administration of the drug is reinstituted after the jaundice is cured, there is no relapse. In one case, Winkelmann was able to find permanent hepatic changes by performing biopsies. Loftus and co-workers[15] described 14 cases of obstructive jaundice; biopsy showed stasis in the biliary ducts with inflammatory infiltration in varying degrees. Laboratory test results were typical of obstructive jaundice, although the clinical picture was similar to that of acute viral hepatitis. It should be noted that there were occasional attacks of nausea and vomiting, symptoms usually alleviated by the drug. Serious cases of this nature are rare. One fatality was reported by Boardmann;[4] the patient in question had a cardiac lesion. The clinician should be familiar with these accidents so as to avoid making the wrong diagnosis of other obstructive jaundices that may lead to surgery. The use of chlorpromazine in patients suffering from hepatobiliary conditions should be attended by caution and strict medical and laboratory supervision.

Stomach Pains. Certain sensitive patients complain of malaise and a burning sensation, as well as other disturbances in the gastric region. Lehmann reported that 8 per cent of his patients presented nausea, anorexia, and gastric malaise. In most cases, with the exception of sensitive neurotics, these disturbances lessen with the eventual reduction in dosage and as the patient becomes accustomed to the drug.

Obstipation. Contrary to the effects of reserpine (which accelerates passage through the intestines), chlorpromazine frequently causes obstipation in patients with previously good intestinal function, and it aggravates habitual constipation. These manifestations are also seen in ambulatory patients. F. Mendes[8] reported a case of ileus and bladder paralysis. The occurrence of diarrhea is rare.

Dry Mouth. This is frequently seen with oral administration of the drug to lucid patients. Initially a poor taste of the drug is also noted. Both these inconveniences are considerably lessened with the gelatin-covered tablets and the administration of liquids; this improvement constitutes an advantage. Appetite generally does not decrease but may be increased (weight increase). There is an increase in diuresis and blood sodium, which may explain the dryness felt by the patients. In rare cases, inflammatory reactions of the parotid gland are seen.

Tissue Irritation. This is seen in the area of intramuscular injection and results in local pain, induration, and sometimes ecchymosis. This reaction has been progressively lessened by the advances made in pharmaceutical techniques (correction of *p*H). No abscesses or other infectious complications were seen. In sensitive patients it is advisable to change to the oral and rectal routes of administration, which have proved nearly always adequate, except in acute psychosis and states of agitation.

Allergic Cutaneous Reactions. It is curious that, although chlorpromazine is an antiallergic agent, it causes contact dermatitis with certain frequency, especially in the hospital personnel handling the tablets. Tusques and Gambs[18] also reported a case of a nurse who contracted dermatitis, although she only handled the bed linen of patients under treatment. These authors also described relapses of chlorpromazine dermatitis through simple contact with other nurses who administered the drug.

Gäde and Heinrich observed a severely pruriginous exanthema in one third of their

female patients, which appeared between the fifteenth and twentieth days of treatment and was most severe on the face, neck, thorax, and arms, and in rare cases covered the entire body. Doses of 400 mg. or more were given. The exanthema disappeared in almost all cases with the interruption of treatment. Two patients presented facial edema. In France, the dermatitis contracted by the hospital staff was considered an occupational hazard. In our experiences in Lisbon, we saw only 1 case of this type.

Psychomotor Activity. A certain inhibition of voluntary movement is sometimes seen. The literature contains rare cases (a larger number being seen with the use of reserpine or with a combination of both drugs) of toxic amyostatic syndromes of the parkinsonian type (hypertonus with "gears," reduction and slowness of movements, hypomimesis, and oily face). In milder cases the syndrome may be alleviated without interruption of treatment or by the use of antiparkinsonian drugs.[10] In cases of greater intensity all signs disappear with the end of treatment. Letailleur and co-workers[14] reported a case of this type with oculogyric crises. Deschamps and Cadoret observed dysarthria with the same frequency as Gäde and Heinrich. Ditfurth[6] reported 12 cases of striae manifestations in 165 patients with parkinsonian signs and oculogyric crises. These effects have not yet proved serious and possibly constitute an important component of the therapeutic activity (lowering of the spontaneous motor impulses and inhibition of the extrapyramidal mechanisms).

Torpor and Coma from Drug Combinations. Chlorpromazine is known to potentiate hypnotics and other nervous system depressants. We saw 1 case in which a previous injection of scopolamine and morphine rendered a dose of 200 mg. of chlorpromazine (usually exceeded without risk) dangerous in 36 hours. A female patient, 61 years old, remained in coma for 36 hours and in a state of torpor for 72 hours. This was accompanied by arterial tensions of 7 cm. (maximum) and 5 cm. (minimum). There was no cold sweat, cyanosis, pallor, or other symptom of collapse. Caffeine was the only active drug. Paraire reported a similar case of a patient with confused dreams of alcoholic origin. Salomon, on the other hand, used chlorpromazine in cases of acute alcoholism with agitation. Vallat and Lepetit have demonstrated the danger of combining chlorpromazine with apomorphine. It can, however, be used in combination with bis (diethylthiocarbamyl) disulfide for the treatment of alcoholism.

It is, therefore, advisable to exert more caution with drug combinations. Chlorpromazine is, however, frequently used by us together with phenergan and sodium amytal to combat the sleep problem. The doses used (150 mg. daily on the average) have been well tolerated in these circumstances.

Changes in Arterial Tension. The lowering of tension in individuals suffering from hypotension may be unpleasant; they begin to feel tired, especially after exercise. This phenomenon becomes more severe when standing erect and may lead to lipothymia. This manifestation is not serious and can be avoided by having the patient lie down for a short time after administration of the drug during the first days of treatment. It abates after the first few days and is more important in the neurotic than in the psychotic patient.

Collapse in Hypertensive Patients. The reduction of arterial tension is greater in hypertensive patients than in normal individuals. Meyer described a fatal case of a patient

suffering from chronic purulent bronchitis with bronchopneumonic focci, mitral sclerosis, and gastric hemorrhages (autopsy findings) in whom the maximum tension fell from 20 to 11 and the minimum from 15 to 9.5. J. Moyer and co-workers[16] found electrocardiographic changes in 2 patients; however, since there was no clear relation between these and chlorpromazine, no clinical significance can be attributed to them.

Tachycardia. This is frequently seen and sometimes becomes unpleasant. As with changes in arterial tension, tachycardia results from suppression of inhibitory mechanisms.

Polypnea. The respiration of patients receiving chlorpromazine is generally ample and slow. But, in neurotics, polypnea and dyspnea associated with anxiety are sometimes seen.

Pallor. This affects the face, the entire skin, and the mucosa without signs of anemia. It is probably caused by vegetative effects. It should not be considered an accident and has no clinical importance.

Paradoxic Hyperthermia. Habitually, there is a certain drop in temperature, which is more marked in febrile patients and in those receiving large doses of chlorpromazine (beware of latent tuberculosis). In patients undergoing prolonged therapy, there are sometimes small thermic rises with temporary peaks that last a few hours, rarely more than 12. These episodes have neither morbid significance nor clinical importance. It was not possible to demonstrate their relationship to tissue irritation in the area of injection or to obstipation. Naturally, any infectious cause must be excluded, the same being true for any other cause that may explain the fever.

Changes in the Blood Picture. Biologic changes produced by chlorpromazine are expressed in the form of slight reductions in the leukocyte count, especially that of eosinophils; these have no clinical significance. Any changes of a more intense and persistent nature must be attributed to other causes. Giacobini reported a case of agranulocytosis (treatment associated with promethazine). A slight increase in sedimentation rate may be seen.

Changes in Blood Coagulation. There is usually a lowered coagulation rate during treatment. When therapy is interrupted, there may be an increase above the normal. If treatment is reinstituted, a further increase may occur, constituting a certain risk; therefore, uninterrupted treatment is recommended, and the blood coagulation time of the patient should be periodically checked.

Phlebitis. Several cases of phlebitis and thrombosis with embolism and consequent infarct have been found (Pauwels, Deniker, and Leitão) and a last one (Labhardt) demonstrated in autopsy findings. Generally, these were cases treated with chlorpromazine in combination with barbiturates (sleep therapy).

Lowering of Resistance to Infection. The literature contains cases of bronchopneumonia, some of which were fatal. There also have been reports of generalized pyoderma and furunculosis.[5] The relationship between these manifestations and chlorpromazine is not always clear. Cases are frequently of older and bedridden patients with circulatory debility. In many cases there are previous lesions or infections that must be taken into consideration, and these patients should be under strict medical vigilance. It is then possible to avoid the majority of these accidents, which in fact are exceptionally rare in institutions where all the rules of medical supervision of patients under treatment are obeyed

Cases of Unexplained Death. Leitão,[1] the junior author, cites other fatal cases reported in the literature (sudden death and death by collapse during sleep therapy with chlorpromazine and hypnotics). Cases of this nature were not seen in patients treated with chlorpromazine alone.

PSYCHOSOMATIC INCIDENTS

Against these accidents and incidents of a somatic nature, we should also consider the incidents (which are not serious) caused by disturbances of the psychosomatic integration of chlorpromazine's pharmacologic activity.

Typical of this condition is the anxiety caused by tachycardia in neurotics and psychopaths. These patients complain of palpitations, anginose pains of the thorax, and dyspnea. They worry about the heart and lack of air and ask that treatment be interrupted.

The same type of anxiety occurs with polypnea. In both conditions, patients can be calmed down and the symptoms eliminated with psychotherapy. Emotional reactions may become unpleasant in cases of iatrogenic interventions. The vegetative reactions may be reduced considerably with the use of barbiturates in small doses.

Of even greater importance is the emotional reaction to the lipothymias and to the fear of orthostatic collapse, frequently seen in ambulatory neurotics, if the precaution of maintaining them in decubitus for one to two hours after ingestion of the drug is not taken. This effect abates after one to two weeks. It may, however, be the cause of alarm and resistance to treatment or intensify the spontaneous symptoms of the same nature. It is rarely seen in cases of psychoses nor is it even noted by the patient.

Even if there are no clear signs of lipothymia from orthostatic hypotension, sensitive patients will suffer such painful sensations as sudden fainting, apprehension and inner tremor, and emptiness and anxiety. These manifestations result in tensions in the patients greater than those that take place in the organism, leading to hypochondriac interpretations and neurotic elaborations (hysteria).

Of similar nature are the asthenic reactions seen during the first days of treatment, which generally aggravate equivalent situations. These include general tiredness, prostration, low mental and physical efficiency, and increased sensation of illness. These signs abate after four to eight days of therapy and may be avoided in sensitive patients by starting treatment with small doses (5 to 10 mg.), given in six daily portions, and by total rest.

Still in the same neurotic sense (anxiety and hypochondria), other signs may be seen and described; these include stomach pains, obstipation, pallor, somnolence, and weakening of vision (Phillips) with daily doses of 250 mg.

The patients present another category of complaints resulting from the drug's favorable activity on the symptoms, for example, the mental vacuum experienced by certain patients suffering from obsessions, asthenia following the reduction of emotional excitability, apathy from the decrease in anxiety, and similar manifestations. These effects demonstrate the necessity of psychotherapeutic support of the drug's activity and of the careful control of dosages so as to obtain gentle and gradual effects in sensitive patients.

In other more complex cases, such as loss of personality, there may be an improvement

of certain factors (anxiety) despite deterioration of the feeling of unreality. Others will suffer a temporary reactivation of symptoms (oneirism and nervous agitation).

Other patients, generally psychopaths, will accept the treatment but simultaneously defend themselves against the reduction of aggressive impulses and of lowered activity. We have observed this mechanism during hypomanic excitation in which the excitation was used to overcompensate habitual insufficiencies. We have also seen this mechanism in cases of psychogenic reactions in which chlorpromazine lowers the individual's means of defense (such as reactions of jealousy or pugnacity). Psychotherapy must attempt to make the patient accept the inertia and passivity produced by chlorpromazine, thereby avoiding secondary psychoreactive excitations.

SUMMARY

The authors describe the accidents and incidents observed with the use of chlorpromazine. As accidents requiring medical attention, they cite jaundice, parkinsonian type syndromes, and certain infectious and circulatory complications.

These accidents are rare and avoidable if the patient is kept under strict medical supervision and if the contraindications are taken into consideration; these include infectious diseases, circulatory debility, vascular changes (phlebitis), hematic and hepatic conditions (such as biliary stasis and hepatic insufficiency), extrapyramidal conditions, and the administration of high doses of hypnotics, alcohol, and other atomizing drugs.

There were no persistent lesions attributable to the treatment. The authors noted secondary activities of somatic and psychologic nature and emphasized the possibility, frequent in neurotics and psychopaths, of disturbances of psychosomatic integration of the pharmacologic activity of chlorpromazine, resulting in unpleasant reactions of anxiety and hypochondria. These reactions may be avoided with the use of psychotherapy; the use of the latter in combination with the biologic activity of the drug is what the authors propose to call "convergent psychosomatic therapy."

RESUMEN

Los autores describen los accidentes observados al usar la clorpromazina, citando sólo como accidentes que requieren atención médica la ictericia, envenenamiento por la administración de combinaciones de drogas, y ciertas infecciones y complicaciones circulatorias.

Estos accidentes son raros, pudiendo evitarse si se mantiene al paciente bajo estricta vigilancia médica y se tienen en cuenta las contraindicaciones. Estas incluyen enfermedades infecciosas, debilidad circulatoria, cambios vasculares (flebitis), estados hemáticos y hepáticos (estasis biliar e insuficiencia hepática), síndromes extrapiramidales, toxicidad y la administración de dosis altas de hipnóticos, alcohol y otras drogas.

No hubo lesiones persistentes atribuibles al tratamiento. Los autores observaron reacciones secundarias de naturaleza somática y psicológica, destacando la posibilidad frecuente en neuróticos y psicopáticos, de desórdenes de la integración psicosomática de la actividad farmacológica de la clorpromazina, resultantes en reacciones indeseables de ansiedad e

hipocondria. Estas reacciones pueden evitarse usando psicoterapia en combinación con esta droga. Ello es lo que los autores llaman "terapia psicosomática convergente."

RESUME

Les auteurs décrivent les accidents et incidents observés avec l'emploi de la chlorpromazine. Comme examples d'accident nécessitant des mesures médicales, ils citent seulement l'ictère, l'empoisonnement par les médicaments combinés, et certaines complications d'infection et de circulation. Ces accidents peuvent être évités si le malade est maintenu sous une stricte surveillance médicale et si les contrindications sont tenues en vue; celles-ci comprenent les maladies infectieuses, la débilité circulatoire, les changements vasculaires (phlébites), les conditions hématiques et hépatiques (stasis biliaire et insuffisance hépatique) conditions extrapyramidales, l'empoisonnement et l'administration de fortes doses d'hypnogènes, d'alcool et d'autres drogues atomisantes.

Le traitement n'a produit aucune lésion attribuable à la cure. L'étude note des activités secondaires de nature somatique ou psychologique et met en relief la possibilité—fréquente chez les malades névrotiques et psychopathiques—de troubles dans l'intégration psychosomatique de l'activité pharmacologique de la chlorpromazine, produisant des réactions désagréables d'anxiété et d'hypochondrie. Telles réactions peuvent être évitées en utilisant la psychothérapie, dont l'association avec l'activité biologique de la drogue et ce que les auteurs appellent la "thérapie psychosomatique convergente."

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In Memoriam

Egas Moniz
1874–1955

The Editors of the JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY regret to report the death on December 13, 1955, of Professor Antonio Caetano de Abreau Freire Egas Moniz, a member of the International Editorial Board of this journal.

Professor Moniz was known the world over for his work on cerebral angiography, which he initiated in 1927, and for his pioneer surgical procedure of prefrontal lobotomy, which he first performed in 1935. He conceived the idea for this revolutionary treatment of psychoneuroses while attending the International Neurological Congress in London, and in 1949, he received the Nobel Prize for this work.

EGAS MONIZ

Professor Moniz was born on November 29, 1874, in Avanca, Portugal, and was educated at the universities of Coimbra, Bordeaux, and Paris. Until 1911 he was professor of neurology at the University of Coimbra, and afterwards he held the chair of Professor of Neurology at the Faculty of Medicine in Lisbon. Other posts included that of director of of the Institute of Neurology for Scientific Investigation and physician at the Hospital of Santa Marta in Lisbon.

His political and diplomatic career included service as a deputy in the Portuguese Liberal Parliamente, Minister to Madrid in 1918, President of the Portuguese Delegation to the La Paz Conference in 1918, and Minister for Foreign Affairs from 1918 to 1919. In 1951, he declined the offer of the Republican and Socialist parties to stand as a candidate in Portugal's presidential election.

Among Professor Moniz's many academic affiliations were membership in the Lisbon Academy of Sciences, the Paris Academy of Medicine, the Brazilian Academy of Letters, the Brazilian Academy of Medicine, the Madrid Academy of Medicine, and Honorary Member of the Royal Academy of Medicine. He was awarded the Grand Cross of Isabella the Catholic of Spain, the Grand Cross of Public Instruction (Portugal), the Grand Cross of Santiago de Espada, and was made a Commander of the Legion of Honor.

His numerous works on neurology and neurosurgery, published in several languages, include *The Neurology of War* (1918), *Cerebral Tumors* (1931), *Cerebral Angiography* (1934), *Tentatives opératoires dans le traitement de certaines psychoses* (1936), *Die cerebrale Arteriographie und Phlebographie* (1940), and *Thromboses and other Obstructions of the Carotids* (1941).

QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

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Incorporating the International Record of Psychiatry and Neurology

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INCORPORATING INTERNATIONAL RECORD OF PSYCHIATRY AND NEUROLOGY

FOREWORD

The purpose of the QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY is to present promptly brief abstracts, noncritical in character, of the more significant articles in the periodical medical literature of Europe and the Americas.

For readier reference, the abstracts are classified under the following general headings:

PSYCHIATRY

1. Administrative Psychiatry and Legal Aspects of Psychiatry
2. Alcoholism and Drug Addiction
3. Biochemical, Endocrinologic, and Metabolic Aspects
4. Clinical Psychiatry
5. Geriatrics
6. Heredity, Eugenics, and Constitution
7. Industrial Psychiatry
8. Psychiatry of Childhood
9. Psychiatry and General Medicine
10. Psychiatric Nursing, Social Work, and Mental Hygiene
11. Psychoanalysis
12. Psychologic Methods
13. Psychopathology
14. Treatment
    a. *General Psychiatric Therapy*
    b. *Drug Therapies*
    c. *Psychotherapy*
    d. *The "Shock" Therapies*

NEUROLOGY

1. Clinical Neurology
2. Anatomy and Physiology of the Nervous System
3. Cerebrospinal Fluid
4. Convulsive Disorders
5. Degenerative Diseases of the Nervous System
6. Diseases and Injuries of the Spinal Cord and Peripheral Nerves
7. Electroencephalography
8. Head Injuries
9. Infectious and Toxic Diseases of the Nervous System
10. Intracranial Tumors
11. Neuropathology
12. Neuroradiology
13. Syphilis of the Nervous System
14. Treatment
15. Book Reviews
16. Notes and Announcements

In fields which are developing as rapidly as are psychiatry and neurology, it is obviously impossible to abstract *all* the articles published—nor would that be desirable, since some of them are of very limited interest or ephemeral in character. The Editorial Board endeavors to select those which appear to make a substantial contribution to psychiatric and neurologic knowledge and which promise to be of some general interest to the readers of the REVIEW. Some articles, highly specialized in character, or concerning a subject already dealt with in an abstract, may be referred to by title only at the end of the respective sections.

A section entitled INTERNATIONAL RECORD OF PSYCHIATRY AND NEUROLOGY is included at the beginning of the journal. The Record Section consists of advanced clinical and experimental reports.

The Psychiatry and Neurology Newsletter was compiled by Doctors Leon Epstein and Francis N. Waldrop.

The Editorial Board at all times welcomes the suggestions and criticisms of the readers of the REVIEW.

WINFRED OVERHOLSER, M.D.
Editor-in-Chief

Psychiatry and Neurology
NEWSLETTER

AMERICAN ORTHOPSYCHIATRIC ASSOCIATION MEETING: The 1956 Annual Meeting of the American Orthopsychiatric Association will be held March 15-17 at the Hotel Commodore in New York City. Preregistration will be required for workshops and panel discussions where registrants will be limited in number.

APPLICANTS FOR CHILD PSYCHIATRY TRAINING: The office of the American Association of Psychiatric Clinics for Children is now acting as a clearing house for applicants for specialized training in child psychiatry in clinics that have been approved as training centers by the Association. The minimum requirements for such training are graduation from an approved medical school, an approved general or rotating internship, and two-years residency training in psychiatry approved by the American Board of Psychiatry and Neurology. Stipends are approximately $3600 per annum, and most clinics have a two-year training period, although a few will consider giving a one-year period of training in special cases. Further information may be obtained from the Association office at 1790 Broadway, Room 916, New York 19, N. Y.

AMERICAN PSYCHOSOMATIC SOCIETY MEETING: On March 24 and 25, the American Psychosomatic Society will hold its 1956 Annual Meeting at the Sheraton Plaza Hotel in Boston.

NEW OFFICERS OF THE AMERICAN ACADEMY FOR CEREBRAL PALSY: At the October, 1955, meeting of the American Academy for Cerebral Palsy, which convened in Memphis, Tennessee, the following officers were elected for 1956: Dr. Margaret Jones of the University of California Medical Center in Los Angeles; Dr. Nicholson J. Eastman of Johns Hopkins Hospital in Baltimore; and Dr. Robert A. Knight of Memphis, Tennessee.

NEW OFFICERS OF THE ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE: The following officers were elected December, 1955, at the Thirty-Fifth Annual Meeting of the Association for Research in Nervous and Mental Disease which was held in New York City: President, Dr. Harry C. Solomon; First Vice-President, Dr. Stanley Cobb; Second Vice-President, Dr. Wilder Penfield; Secretary-Treasurer, Dr. Rollo J. Masselink; Assistant Secretary, Dr. Lawrence C. Kolb.

NEW JUNGIAN PSYCHOLOGY JOURNAL: The London Society of Analytical Psychology has launched a new publication called

the Journal of Analytical Psychology to publicize the work of the Jungian school. It is published by Tavistock Publications, Ltd., 2 Beaumont Street, London, W. 1, at the price of 12s. 6d. per issue.

NEUROLOGY TRAINING PROGRAM: The American Board of Psychiatry and Neurology announced its approval of a two-year training program in neurology at the Veterans Administration Hospital in Oakland, California. Dr. J. K. Smith is the full-time program director, and the visiting staff includes Dr. Walter F. Schaller, Dr. Knox Finley, and Dr. Leon Whitsell. Inquiries and communications relating to the program should be sent to Dr. William R. Haas, Veterans Administration Hospital, Oakland, California.

SPECIAL COURSE FOR GENERAL PRACTITIONERS: The American Academy of Neurology announced a special course for general practitioners that will cover the developments in diagnosis and treatment of common neurologic disorders. The subjects will be presented by a qualified member of the American Academy of Neurology and will cover headaches, strokes, parkinsonism, neurologic emergencies, disorders of muscle, and paraplegic states. Applications and inquiries should be sent to Mrs. J. C. KcKinley, AAN Executive Secretary, 3501 East 54 Street, Minneapolis 17, Minn.

INTERNATIONAL COLLOQUIUM ON CHLORPROMAZINE AND THE NEUROLEPTIC DRUGS IN PSYCHIATRIC TREATMENT: This International Colloquium, which was held in Paris, October 20-22, 1955, was attended by more than 300 psychiatrists, psychologists, and physiologists from practically all the countries in Western Europe, North Africa, and the Americas.

The readers presented the results of their experience with reserpine and chlorpromazine. The numerous papers cannot be summarized here; they will be published in a special issue of L'Encephale and will constitute a useful addition to our knowledge of these drugs.

Professor Jean Delay, who presided over the colloquium, remarked that the value of the drugs is agreed in that they aid in the psychologic and social treatment of the patient, these latter forms of treatment being fundamental. He expressed, as did Professor Heuyer and others, a preference for the term "neuroleptic" as against "ataraxic." The latter, he commented, is a philosophic term that is too general, since an "absence of disordered emotion" can be obtained with opium, for example. The former, however, emphasizes the neurologic and physiologic basis of the psychologic change that is brought about by the drugs.

QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

A Controlled Study of Chlorpromazine Therapy in Chronic Psychotic Patients

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WASHINGTON, D. C.

Chlorpromazine hydrochloride* is a relatively new depressant drug. It was synthesized by Laborit of France while he was studying a series of dibenzoparathiazine derivatives in order to determine which of these might be used to enhance the action of general anesthetics. It was then noted that the drug tended to produce general psychomotor retardation while the sensorium and all intellectual functions remained clear and intact. Although Laborit at first used chlorpromazine in surgery as a means of facilitating general anesthesia, he later used it in human subjects in whom he could induce a somnolent state, which he termed "artificial hibernation." His work subsequently renewed the interest of European psychiatrists in treating patients with sleep therapy. This led to intensive investigations by Delay and Deniker,[4] who found that the drug is useful in controlling psychomotor agitation and in treating various psychoses.

Since chlorpromazine has been introduced in the United States, its pharmacology has been extensively investigated. In the light of our present experimental and theoretic neurophysiologic knowledge, Lehmann[9] has fully discussed its probable site and manner of action. According to his discussion of the subject, the essential action of chlorpromazine is inhibitory. Chlorpromazine appears to have the property of "selectively reducing all action tendencies whose origin and maintenance are principally dependent on feelings." When the drug is given in adequate dosage, it produces extreme sedation without significant intellectual clouding. Analyses of the action of chlorpromazine on the central nervous system furnish ample evidence for the assumption that its site of action is in parts of the brain stem, particularly in the subthalamic nucleus, red nucleus, substantia nigra, hypothalamus, and the reticular formation. Recently, the reticular-activating system (reticular formation) in the brain stem has been shown to be responsible for the state of wakefulness

* The trade name of Smith, Kline & French Laboratories for chlorpromazine is Thorazine. The chlorpromazine used in this study was supplied through the courtesy of Smith, Kline & French Laboratories, Philadelphia, Pa.

and attention upon which most higher functions of the central nervous system depend. The data which Lehmann has presented may serve to explain some of the desirable effects that many psychiatric patients have when they are under the direct influence of the drug.

Since the drug's introduction in Europe and later in the United States, it has been widely investigated as a therapeutic agent in the treatment of psychoses and neuroses. A number of investigators[3, 6] who have reported on the use of chlorpromazine in treating neurotic patients have asserted that it tends to alleviate, and in some cases even abolish, their presenting neurotic symptoms. However, in the many published articles relating to the effectiveness of chlorpromazine treatment in certain psychotic syndromes, these investigators apparently have been even more favorably impressed with the various degrees of improvement observed in the majority of such patients. Many of them, however, have wisely reserved ultimate judgment on the effectiveness of chlorpromazine treatment in certain psychoses until the drug is allowed a much longer term of trial.

With respect to the subject of chlorpromazine therapy in psychotic patients, an attempt has been made to review the literature which had been published prior to collecting the data of our own chlorpromazine project. In these chlorpromazine studies the occurrence of one or more of the following significant omissions has often made the reader's interpretation of the results quite difficult or equivocal. These omissions especially pertained to the following questions: What constituted effective dosages of the drug, and what were the investigators' criteria upon which they based the conclusion that an effective dosage had been reached in their individual patients? In the various psychoses brought under study, what were their correlations between duration of treatment and efficacy of treatment? What were their specific criteria which permitted them to place their patients in their various categories of improvement?

In addition, the specific diagnoses of the patients who had been brought under study was frequently not explicitly denoted. Nevertheless, we present the following short summaries of some of the more important articles which have been published on the subject.

Azima and Ogle[2] administered chlorpromazine to 27 cases of schizophrenia, 5 cases of mania, and 5 cases of agitated depression. All of these patients had suffered from an initial acute onset of their psychoses or suffered from a recent remission. The patients received an average dose of 400 mg. of chlorpromazine daily for a period of 21 days. They reported that no significant change was observed in the nonexcited patients of the schizophrenic group. In all of the tense, excited, and impulsive schizophrenics a moderate reduction o- their symptoms appeared in addition to their having improved ward behavior and socializaf tion. In most cases, such improvement apparently persisted after the drug had been discontinued. Of the 5 manic patients, 3 recovered, but the other two remained unchanged. Moderate improvement was noted in 3 of the 5 depressed patients. However, the symptoms of these 3 patients returned after they had stopped taking the drug.

In the acutely psychotic person and especially the paranoid schizophrenic, Kelly[7] reported that chlorpromazine frequently produced a complete remission of symptoms. He considered the drug as being very successful in its application to those patients who are

extremely hyperactive. Furthermore, he stated that many chronic schizophrenics improved considerably with chlorpromazine, even though they did not fully recover.

After having studied the effects of chlorpromazine in 50 patients, Anton-Stephens[1] wrote in a preliminary report that in his series, the responses to the drug had varied. He remarked, however, that chlorpromazine especially produced a lessening of disturbed behavior in schizophrenic and manic excitements of the studied patients, and the ease with which such states were amenable to the drug was quite remarkable.

Kinross-Wright[8] reported one series of 30 schizophrenic patients treated with chlorpromazine. Although he did not give the details of this sort of therapy in these patients, he stated, "The situation two months after the conclusion of treatment was as follows: Eight were at home and symptom-free, 13 were much improved with most of them living at home, five were somewhat improved, and four were no better." After having treated depressed patients with chlorpromazine, he reported that the results with such patients had been more variable. Though he wrote that he had many successes in having treated these patients with the drug, he concluded, nevertheless, that electroconvulsive therapy remains the treatment of choice in this group.

Bower[3] studied 29 cases, among whom were included 12 manics, 7 schizophrenics, and 5 cases of depression. On the basis of his observations, he concluded that chlorpromazine's greatest value is for patients with acute symptoms of increased psychomotor activity. He reported that in chronic patients, chlorpromazine induces calm without significantly changing mental content, but the drug does seemingly diminish the frequency of their hallucinations. He further observed that depressed patients did not respond well to chlorpromazine.

Elkes and Elkes[5] studied 27 agitated, chronically psychotic patients. Thirteen were schizophrenics, 11 belonged to the "affective group," and 3 belonged to the "senile group." Seven of these patients showed definite improvement, and 11 manifested only slight improvement. While they were receiving chlorpromazine, apparently all became less tense and less disturbed by their hallucinations and delusions. Also, they were more amenable to the suggestions and care of the nursing staff. Elkes and Elkes believed that the affective group appeared to respond slightly better than the schizophrenic one.

In Winkelman's[11] study of 142 patients, of whom 75 were psychotic, he presented several observations and conclusions. As the result of this therapy, severe anxiety and tension states were markedly reduced, and they were often replaced with a sense of well-being. With long-term treatment (three to six months), the beneficial effects of chlorpromazine usually persisted for periods ranging from two to five months after the drug had been discontinued. He stated that this drug is not only remarkable in that it can reduce severe anxiety but that it can also reverse or modify a paranoid psychosis and quiet manic or extremely agitated patients. He further remarked that it should not be considered merely a chemical restraint that has no real effect on the patient's illness. Instead, chlorpromazine should be considered a true therapeutic agent, but one which has definite indications.

Since most of the studies on the use of chlorpromazine were conducted without the utilization of controls, it was decided that in this case, emphasis would be placed on the comparison of chlorpromazine therapy with the administration of placebos.

The study was conducted on 100 patients who were carefully picked by the authors and transferred to two wards where they were kept for two weeks prior to the onset of therapy. The patients were all Negro women and were considered disturbed. They were divided into two distinct groups in such a manner that each patient in group T had a similar counterpart in group C. As far as possible, the patients were paired according to age, duration of illness, diagnosis, and behavior. Twenty-five patients from group T with their partners from group C were then placed on one ward, and the other 50 patients were kept on the other ward. The ward personnel was cautioned against giving the patients extra attention, as was done in studies conducted in other parts of the hospital. This eliminated the psychotherapeutic factor which has frequently been considered the real reason for the efficacy of the drug. During the preliminary two week period, the patients were carefully observed by the nursing staff, and detailed notes were written in each chart, including the ward behavior of the patient, weight, temperature, blood pressure, catamenial record, appetite, and sleeping habits. At the same time, each patient was subjected to a thorough mental examination similar to the progress note to which most of the patients were accustomed. A complete physical examination, including any necessary laboratory studies, was done on each patient. They were then informed that on February 14, 1955, they would be started on a new medicine.

All patients in group T received chlorpromazine T, and those in group C received chlorpromazine C, a specially prepared placebo which was indistinguishable from the drug. The ward personnel and the patients were not informed of the difference in the two preparations; the medication was dispensed by the nurse supervisor, who was not a ward nurse. Each Monday, a group of 5 T and 5 C patients were started on the drug therapy until, at the end of five weeks, all 100 patients were receiving either one of the two preparations.

The ages of the patients ranged from 8 to 57 years; the duration of illness ranged from 1 year to 24 years. Some of the patients had had other forms of therapy prior to the present study, and in most cases it was electroshock and/or insulin subshock therapy. The 13 different diagnoses in the 100 patients were as follows: chronic brain syndrome with meningoencephalitic syphilis, 4; involutional psychotic reaction, 1; manic-depressive reaction, manic type, 4; schizophrenic reaction, 89, including 4 hebephrenics, 44 catatonics, 27 paranoids, 1 acute undifferentiated, 9 chronic undifferentiated, 1 schizoaffective, 2 childhood type, and 1 unspecified schizophrenic; psychotic disorder with mental deficiency, 1; and psychotic disorder, undifferentiated, 1.

CLINICAL PROCEDURE

The individual patient dosage was prescribed daily by the authors. All the patients received the same parenteral dose for the first three days of therapy: 50 mg. on the first day, 100 mg. in two doses on the second day, and 150 mg. in three doses on the third day. All injections were given intramuscularly and consisted of 1 ml. of the drug with 1 ml. of isotonic saline. The sites of injection were the right and left deltoids, right and left buttocks, and right and left lateral aspect of the thighs. After the third day, the patient received all medication orally, unless he refused to swallow the tablet or was found to be disposing

of it in some other way. The nurses were warned to examine the patient's mouth carefully in case the tablet was secreted and not swallowed. If a patient was found to be "cheating," one injection (consisting of one-half the oral dose) was administered, and in all cases this was sufficient to convince the patient that oral medication was preferable.

On the fourth day, each patient received 150 mg. or 300 mg. orally in three doses, depending on her initial response to the intramuscular medication. This dosage was continued for five days, after which the dosage was increased by 50 or 100 mg. every five days until maximum improvement was obtained. The highest maximum dose was 900 mg., and the lowest was 300 mg. For this study, the duration of therapy was varied from group to group in order to determine the optimum time. Thus the duration varied from 16 to 116 days. Treatment was terminated by reducing the dosage by 50 mg. daily until the end.

During the observation period, no other medication was prescribed, and, since all cardiac and diabetic patients were excluded from the study, this rule was followed without difficulty. No sedatives were administered at all during the treatment period, and, except for occasional laxatives, enemata, and two instances of penicillin therapy for acute infection, it was not found necessary to prescribe other medications. The patients were not permitted to leave the ward for the first two weeks of therapy, except for clinic appointments. After two weeks, privileges were granted to patients whenever they were considered ready for them. Home visits were not permitted until the therapy was terminated. However, ground privileges were granted towards the end of the therapy. Occupational therapy was prescribed for all patients who showed an interest in it, and many of them were permitted to keep their work with them at all times, but scissors, needles, and crochet hooks had to be returned to the nurses' office at bedtime.

Regular diet was prescribed, and the patients were encouraged to rest in bed during the first week of therapy, after which they were permitted to rest in bed whenever they felt like it. Temperature, pulse, respiration, and blood pressure were charted twice daily for three weeks, daily for two weeks, and then only as indicated. Weight and catamenial records were kept monthly, and nurses' notes were written daily for 10 days and three times a week for the duration of the treatment. All unusual occurrences were noted.

After the tenth day, any rise in temperature was a signal for the following laboratory tests: liver function test (icterus index, cephalin flocculation time), white blood count and differential, and urinalysis for urobilinogin. A very close observation was maintained at all times to discern signs of jaundice or parkinsonism. All complaints, however trivial, were immediately reported to the authors and investigated. In most cases verbal reassurance was sufficient, but, in a few cases where complications arose, the patients were transferred to the medical and surgical service for observation and treatment. Wherever possible, chlorpromazine therapy was continued under the supervision of the internist or surgeon.

Weekly meetings were held with the ward personnel to further their understanding of the drug therapy and to allay their anxiety. Frequent interviews were held with the relatives of the patients for similar reasons. Every effort was made to keep the doctor-patient relationship on the same level as prior to the therapy.

Since the treatment of the control group was identical with that of the T group, whenever

TABLE I

Results of Chlorpromazine Therapy

Status	T patients	C patients
Recovered	3	0
Marked improvement	10	0
Moderate improvement	7	1
Slight improvement	18	3
Unchanged	10	45
Worse	2	1

an order was written for a T patient, her C partner received the same order. As each couple was terminated, the C patient was started on chlorpromazine T the following Monday. The same procedure was followed, and in this way every control had a double set of results, the first being with the placebo and the second with the regular drug.

RESULTS

The authors consider that one of the reasons why there has been a variation in the results of chlorpromazine therapy is that the terms used to describe the patient's condition have different meaning to the individual investigators. It was therefore decided to set up a standard by which our patients would be judged, and then all personnel involved in this project would have an objective, rather than a subjective, criterion for evaluating results. The following terms were to be used, and their definitions were given as follows:

(1) Recovered: no abnormal content; presence of real insight. (2) Marked Improvement: abnormal content present; good social adjustment, including ground parole, home visits. (3) Moderate Improvement: abnormal content present; transfer to better ward; supervised privileges. (4) Slight Improvement: abnormal content present; improved ward behavior; no privileges. (5) Unchanged. (6) Worse.

At the conclusion of the therapy, each patient was given a thorough mental examination and was evaluated by several people. The results were then discussed. The conclusive results in table I were accepted as the status of the patient immediately following the last dose of chlorpromazine T or C.

It became immediately apparent that chlorpromazine produced a definite reaction in the patients and that the 50 controls did not need to be included in the further breakdown of the results. The subsequent tables which were compiled were confined to the 50 patients who had received the drug and not the placebo. The 4 controls who showed a slight change apparently responded to the psychologic effect of medication, the attention they received when having their blood pressures checked, and the taking of the actual injections or tablets.

Special attention was paid to the development of complications, and these were charted for each patient with the date of onset. Four patients had to be terminated before the end of therapy because of severe complications requiring transfer to the medical and surgical departments. One patient developed slight urticaria on the ninth day, which became

generalized on the sixteenth day, when therapy was stopped. One patient developed jaundice on the twenty-first day, which necessitated discontinuance of therapy; and 1 patient developed marked symptoms of parkinsonism on the twenty-eighth day, and therapy was stopped on the following day. One patient developed a fever of 105.4 F. and a blood pressure of 190/100 mm. of mercury on the sixteenth day, when therapy was discontinued.

The complications were frequent but not severe. Only 16 patients out of the 50 in group T had no complications. The most frequent complication was lactation which occurred in 18 patients, usually about the eleventh day. Most patients had more than one complication. The complications are summarized in table II.

Following the compilation of available data, a series of charts were drawn, which will be discussed later. The most significant result of the chlorpromazine therapy was noted in the difference of response on the two wards. This was attributed to the personalities of the nurses and attendants, since their enthusiasm for the drug varied in intensity. Patients receiving the drug from personnel who were very enthusiastic and optimistic seemed to derive greater benefit from the medication. When the project was well under way, the entire service was involved in the annual chest roentgenogram survey. Whereas the rest of the service required liberal sedation, the chlorpromazine patients, with the exception of the controls, required little or none. On the whole, the two wards underwent a phenomenal change of character, being transformed into quiet, cooperative wards from previously violently disturbed wards. The special treatment rooms, which had been previously in great demand, stood vacant most of the time and were finally converted into private rooms.

The over-all results have been tabulated, table III incorporating all conceivable factors which might have influenced the response to chlorpromazine.

DISCUSSION

In table III it can readily be seen that the age of the patient has little or no effect on the response to the drug. In the same category can be placed the duration of illness. Previous

TABLE II

Complications Occurring with Chlorpromazine Therapy

Complication	T patients	
	No.	Per cent
Lactation	18	36
Fever	12	24
Drowsiness	5	10
Hypothermia	4	8
Tremors	4	8
Fainting	2	4
Jaundice	1	2
Parkinsonism	1	2
Urticaria	1	2

TABLE III

Over-all Results of Chlorpromazine Therapy

Pt.	Age	Diagnosis*	Durat. illness, yrs.	Prev. therapy†	Durat. treatment, days	Max. dose, mg.	Av. dose, mg.	Complications‡	Response
T4	32	22.2	3	—	59	750	250	Lactation (32)	Recovered
T26	31	22.2	7	—	44	500	300	Lactation (11)	Recovered
T10	52	22.3	7	ISS	50	800	450	—	Recovered
T1	36	21.0	2	—	51	700	400	Diarrhea (4), drowsiness (9)	Marked improvement
T21	29	21.2	2	—	46	600	200	Lactation (11), tremors (21)	Marked improvement
T6	24	22.1	2	—	53	600	400	—	Marked improvement
T11	30	22.2	6	20 EST	45	400	300	Drowsiness (11)	Marked improvement
T33	21	22.2	1	30 EST	43	550	300	Lactation (11)	Marked improvement
T44	31	22.2	4	40 EST, Psy. Rx	43	550	300	Lactation (11), fever (9)	Marked improvement
T13	39	22.3	4	—	55	900	350	Lactation (17)	Marked improvement
T25	48	22.3	4	20 EST	42	500	300	Constipation (26), hypopyrexia (29)	Marked improvement
T46	34	22.5	8	30 ISS, 15 EST	43	550	300	Drowsiness (14)	Marked improvement
T23	49	22.6	6	—	17	500	350	Hyperpyrexia (16)	Marked improvement
T9	46	11.01	17	Antiluetic Rx	50	800	450	Lactation (25)	Moderate improvement
T12	29	22.2	2	43 ISS, 15 EST	47	600	200	Fever (11)	Moderate improvement
T18	42	22.2	18	ISS, EST	43	300	250	Fever (16)	Moderate improvement
T3	41	22.3	1	—	46	600	350	Fever (7), lactation (22)	Moderate improvement
T24	39	22.3	7	—	44	600	350	Lactation (18), hypopyrexia (18)	Moderate improvement
T37	36	22.3	9	—	107	900	600	—	Moderate improvement
T38	36	22.3	5	Psy. Rx	44	600	350	—	Moderate improvement
T8	34	22.1	4	15 EST	50	800	450	Lactation (25), fever (8), tremors (34)	Slight improvement
T2	35	22.2	3	—	21	400	250	Fever (2), lactation (17), jaundice (21)	Slight improvement
T16	31	22.2	4	27 EST	55	900	500	Fever (4)	Slight improvement
T27	27	22.2	7	2 EST	53	700	350	Lactation (11)	Slight improvement
T28	30	22.2	1	15 EST	44	600	350	—	Slight improvement
T29	37	22.2	13	30 ISS	49	500	350	Lactation (11)	Slight improvement
T30	39	22.2	4	14 EST	51	700	400	—	Slight improvement
T35	42	22.2	7	22 EST	116	900	600	—	Slight improvement
T39	27	22.2	2	7 EST	77	600	450	—	Slight improvement
T40	22	22.2	1	EST	104	750	550	—	Slight improvement

(Table continued on next page)

TABLE III (*Continued*)

Over-all Results of Chlorpromazine Therapy

Pt.	Age	Diagnosis*	Durat. illness, yrs.	Prev. therapy†	Durat. treatment, days	Max. dose, mg.	Av. dose, mg.	Complications‡	Response
T41	32	22.2	3	31 ISS, 16 EST, Psy. Rx	42	500	250	Constipation (6)	Slight improvement
T20	41	22.3	22	—	47	500	300	—	Slight improvement
T49	24	22.3	3	—	43	550	300	Hypopyrexia (5), dizziness (21)	Slight improvement
T7	28	22.5	5	—	29	700	450	Lactation (25), parkinsonism (28)	Slight improvement
T43	42	22.5	4	—	41	450	300	—	Slight improvement
T45	35	22.5	4	—	42	550	300	Fever (10)	Slight improvement
T32	15	22.7	3	—	43	550	300	Lactation (8)	Slight improvement
T19	34	22.9	2	—	49	600	350	—	Slight improvement
T50	51	11.01	7	11 EST	44	600	350	Fever (10)	Unchanged
T22	25	22.2	2	12 EST	53	900	300	Fever (3), lactation (11)	Unchanged
T34	36	22.2	3	15 EST	43	550	300	—	Unchanged
T36	39	22.2	2	—	46	700	450	—	Unchanged
T42	29	22.2	2	3 EST	42	500	300	Fever (10, 24)	Unchanged
T17	37	22.3	4	30 ISS, 17 EST	49	600	350	Lactation (18), tremors (37)	Unchanged
T47	52	22.3	22	—	44	600	350	Fever (4, 16), fainting (23)	Unchanged
T48	49	22.3	10	—	45	700	450	—	Unchanged
T5	39	22.5	7	36 EST, ISS	59	750	250	—	Unchanged
T31	38	22.5	2	—	38	300	250	Tremors (11)	Unchanged
T15	30	22.2	4	30 ISS, 16 EST	52	700	350	Lactation (18)	Worse
T14	55	20.	1	—	16	300	200	Urticaria (9), hypopyrexia (11)	Worse

* 11.01: Meningoencephalitic, central nervous system syphilis with psychotic reaction.
20.0: Involutional psychotic reaction.
21.0: Manic depressive reaction, manic type.
21.2: Manic depressive reaction, depressive type.
22.0: Schizophrenic reaction, simple type.
22.1: Schizophrenic reaction, hebephrenic type.
22.2: Schizophrenic reaction, catatonic type.
22.3: Schizophrenic reaction, paranoid type.
22.5: Schizophrenic reaction, chronic undifferentiated.
22.6: Schizophrenic reaction, schizoaffective type.
22.7: Schizophrenic reaction, childhood type.
22.9: Schizophrenic reaction, other.

† ISS signifies insulin subshock therapy; EST, electroshock therapy.

‡ Figures in parentheses indicate day of onset of complications.

therapy seems to have little, if any, effect, and the presence or absence of complications throws no light on the individual response to therapy.

Chlorpromazine must have some effect on patients, since 38, or 76 per cent, of the patients showed slight improvement to recovery after receiving it, while only 4 showed any improvement on the placebo. Whereas 45 patients, or 90 per cent, of the controls remained unchanged, only 10 patients, or 20 per cent, of the chlorpromazine patients were unchanged.

Our results indicate clearly that involutional psychotic reaction is not to be treated with chlorpromazine. This is apparently in accord with the findings of others and therefore is not an unexpected result. General paresis does not seem to respond to chlorpromazine, although one of the patients showed a moderate improvement. This was not sustained and, immediately following withdrawal of the drug, she lapsed back into her usual noisy, assaultive behavior. Chlorpromazine in this case appeared to act as a superior sedative whose effect was not lasting but immediate. The manic-depressive psychoses, on the other hand, responded extremely well to the drug, as both manic patients showed marked and sustained improvement with considerable insight several months after cessation of therapy. The remaining 45 patients were schizophrenics and will be discussed separately.

It is most significant that the 3 patients who recovered were all schizophrenics (2 catatonics and 1 paranoid). Of the other types, the schizoaffective had the best response, although all the others showed some improvement. Of the 6 chronic undifferentiated types, 2 remained unchanged and the other 4 showed some response.

Of the 22 catatonics, 9 per cent had complete recovery, 14 per cent showed marked improvement, 9 per cent had moderate improvement, 45 per cent had slight improvement, 18 per cent were unchanged, and 5 per cent became worse. Of all the schizophrenics, the catatonic has the best prognosis with any form of recognized therapy. It is therefore to be expected that the majority of catatonics would respond to chlorpromazine. The paranoid, however, has always been considered as having a very poor prognosis. In examining our results with paranoids, we find that of the 12 paranoids included in our study, 8 per cent showed complete recovery, 17 per cent were markedly improved, 33 per cent were moderately improved, 17 per cent were slightly improved, and 25 per cent remained unchanged. This is most encouraging, for if 25 per cent of paranoid patients treated with chlorpromazine showed marked improvement or complete recovery, the value of the drug is greatly increased. Mental hospitals are usually filled to capacity with paranoids who cannot be discharged, and the addition of chlorpromazine to the hospital armamentarium becomes a shining light in a previously dark area. We can thus conclude that chlorpromazine is useful in the treatment of manic and schizophrenic patients, particularly paranoid and catatonic, but is contraindicated in involutional patients.

There is no apparent relationship between duration of illness and response to therapy. The duration of illness need not concern the therapist when contemplating the use of chlorpromazine for the treatment of the previously mentioned psychoses.

Although the best response seemed to be after 40 to 60 days of therapy, a good response was obtained after less than 20 days of treatment. It was quite apparent during the study that if there was no response after 50 days, none could be expected from prolonging treat-

ment. The conclusion was reached that duration of therapy should be determined by the response of the individual patient and need not be over 50 days if no response is noted.

Good results were obtained with almost every dosage. Again, the dosage must be determined by the response of the individual patient and cannot be considered inflexible.

The presence or absence of complications, as well as their severity, has absolutely no bearing on the response of the patient to chlorpromazine. Lactation occurred in every one of the six response categories. It also antedated the two most severe complications, jaundice and parkinsonism. Laboratory tests on the specimens obtained from the lactating patients showed colostrum in all cases and pure milk in 1 case. This condition occurred in young nongravid patients as well as in postmenopausal patients and therefore must be considered a direct result of chlorpromazine therapy. Its significance has not been determined in this study, although it stimulated an independent investigation of the physiologic and biochemical changes during chlorpromazine therapy, which will be reported later.

All complications subsided following termination of therapy, and none of the patients appeared to have suffered any ill effects from the drug. The termination of therapy for jaundice, parkinsonism, hyperpyrexia (105.4 F.), and generalized urticaria was due to the conservative attitude of the hospital administration and not because of any threat to the patient's life. On the whole, the complications were insignificant and rarely required specific therapy.

The study was therefore successful in demonstrating the efficacy of chlorpromazine therapy in chronic psychotic patients, the comparative lack of serious side effects, and the important psychologic effect on the hospital personnel, which eventually resulted in better management of the patients.

The study also demonstrated a further need for investigating the effect of chlorpromazine after discontinuance of therapy, the incidence of relapses, and whether a patient will require maintenance doses for long periods of time, or if one successful course of therapy will be sufficient. There is also a need to discover if the serious complications such as jaundice and parkinsonism can be predicted by laboratory tests, and if they can be prevented, and if there will be permanent damage to the liver and the brain if therapy is continued.

SUMMARY AND CONCLUSIONS

To determine the efficacy of chlorpromazine therapy, a controlled study was started, using 50 Negro women psychotics and 50 similar controls. The entire project was rigidly controlled to prevent extraneous factors such as psychotherapy, additional attention, and increased privileges from obscuring the effect of the drug. The dosages and length of drug therapy were individualized for each patient. Careful mental examinations were conducted at the beginning and the end of the project. Standard criteria were set up for determining the response of the patient. Six charts were drawn up to compare the response of the patients to all conceivable factors which might influence such a response, and these were discussed.

The following conclusions were drawn from the study: (1) Chlorpromazine is effective in the treatment of chronic psychotic patients, since 90 per cent of the controls remained

unchanged as compared to 20 per cent of the patients on chlorpromazine. (2) The age of the patient, duration of illness, and previous therapy have no effect on the response to the drug. (3) Chlorpromazine is not effective in the treatment of involutional psychoses or general paresis. (4) It is most effective in the treatment of manic and schizophrenic patients, particularly catatonic and paranoid, although the other types showed some response. (5) The most effective dose and duration of therapy must be determined for the individual patient by trial and error method, but from all indications if there is no response after six weeks of therapy, there will probably not be any response from prolonging the treatment. (6) Most of the patients had some slight effects, such as drowsiness, temperature elevations, constipation, and tremors. None of these required specific therapy. More severe complications included lactation, fainting, hyperpyrexia, urticaria, parkinsonism, and jaundice. The last four complications resulted in immediate termination of therapy without lasting ill effects. Of 50 patients, only 4 or 8 per cent required discontinuance of therapy. The presence or absence of complications had no effect on the response to the drug. (7) The over-all effect of the project resulted in raising the morale of the hospital personnel and the patients' relatives, so that management of patients improved and many more were permitted privileges. In spite of all precautions, the psychologic effect of chlorpromazine could not be eliminated. (8) Two catatonics and 1 paranoid patient completely recovered from their psychoses after having been psychotic for as long as seven years. (9) Further clinical and laboratory investigation is necessary before chlorpromazine can be used with complete confidence in the treatment of chronic psychotic patients.

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ABSTRACTS

psychiatry

ADMINISTRATIVE PSYCHIATRY AND LEGAL ASPECTS OF PSYCHIATRY

1. *The Doctor in Court.* HUMPHRY OSMOND, Weyburn, Canada. Canad. M. A. J. *73*:40–44, July 1, 1955.

Some of the common hazards that beset the doctor in the witness box and suggestions as to how they may be avoided are described. Many difficulties may arise from inadequate preparation and the failure to make proper notes at the time the patient or prisoner was seen. The law allows one to refer to written notes taken at this time. Before giving evidence, it will be easier to follow the proceedings if one is acquainted with the legal phrases commonly used in court.

The doctor may be called on as a witness of fact or of opinion. If he is being asked about facts, then he may only state what he himself has heard or seen. Witnesses of opinion have far more latitude, but as a wise judge said recently: "The opinion of an expert witness carries as much weight as his reasons for holding that opinion."

Once in the witness box, the doctor, having identified himself to the court, taken the oath, and given an account of his qualifications, should adjust his voice so that the furthest juryman can hear without difficulty. Speech should be slow and clear, and medical jargon should be avoided. A better impression will be made if the dress and demeanor fit in with the layman's conception of a doctor. We must, therefore, make every effort to appear sober and professional.

Examination by the counsel of the side for which the doctor is appearing is followed by cross examination by the counsel for the other side. Lawyers employ various methods in cross examination, such as hectoring, a honeyed tongue, letting the witness talk himself out of everyone's patience, and getting him to antagonize the court actively and lose his temper. All these can be avoided by care, deliberation, and forethought. It is important when in court not to blurt out the first thing that comes to mind but to ponder a little.

While the doctor must learn his way about law courts, he must remain a doctor and not identify himself so closely with legal procedures that he loses his medical viewpoint. The medical man should make his own special contribution to justice and allow the lawyers to decide how it stands in law. Medicolegal societies are excellent ways to discuss differences and develop areas of agreement.—*Author's abstract.*

ALCOHOLISM AND DRUG ADDICTION

2. *Acceptability for Psychotherapy in Institutionalized Narcotic Addicts.* ALAN MCLEAN, JACK MONROE, STANLEY YOLLES, HARRIS HILL, AND H. ALAN STORROW, Lexington, Ky. A. M. A. Arch. Neurol. & Psychiat. *74*:356–362, October, 1955.

The purposes of the present study were to isolate characteristics of narcotic addicts that

influence the psychiatrists' judgments of acceptability for psychotherapy, to estimate the percentage of a defined addict population that might be considered acceptable for psychotherapy, and to determine the extent to which such acceptability can be defined in terms of measures derived from psychologic data, sociologic material, and nonpsychiatric interviews. The objective was, in part, to develop a uniform screening procedure to increase the likelihood of selecting acceptable patients for therapy.

Accordingly, 100 institutionalized addict patients were evaluated, first, by a specially devised social service questionnaire; second, by a psychiatric social worker's interview; third, by a battery of psychologic procedures; fourth, by judgments of a board of three staff psychiatrists; and fifth, by a brief trial period in psychotherapy.

The therapists' judgment of acceptability was the criterion with which the psychologic tests, the social service interview, and the social service questionnaire were correlated.

Each patient was started on the various procedures approximately one week after withdrawal from narcotics was completed, and all procedures were carried out during a two week period, the first week being devoted to social service evaluations and psychologic testing, and the second to psychiatric examination and the trial period in therapy. Processing was completed on each subject by the twenty-ninth day of his hospitalization.

The psychotherapists' evaluations resulted in their terming 46 patients acceptable and 54 less acceptable for therapy. Among the more significant reactions that the therapists felt contributed to their judgments were the patient's ability to verbalize feelings as well as ideas, evidence of original thinking, and spontaneous verbal production in problem areas. Patients in the acceptable group were also more apt to ask for aid with their problems and showed more evidence of previous ability to modify their patterns of living.

Estimates of acceptability made by psychiatric social workers based upon a formal social service questionnaire as well as on the unstructured hour-long interview correlated significantly with the psychotherapists' judgments. Certain psychologic measures, including tests of verbal intelligence and degree of manifest anxiety, were significant predictors of acceptability. Finally, various combinations of screening procedures demonstrated that patients judged to be more acceptable for therapy by psychiatrists could be selected with a high degree of accuracy from a larger group of patients by social service interviews and psychologic tests. 10 references. 1 table.—*Author's abstract.*

BIOCHEMICAL, ENDOCRINOLOGIC, AND METABOLIC ASPECTS

3. *Adrenochrome as the Cause of Schizophrenia: Investigation of Some Deductions from this Hypothesis.* A. J. LEA, Bispham, Lancs, England. J. Ment. Sc. *101*:538–547, July, 1955.

Hoffer, Osmond, and Smythies have implicated adrenochrome or some related substance as the cause of schizophrenia, i.e., schizophrenia is due to an abnormality of tyrosine metabolism. From this it was deduced that schizophrenics should show (a) an excess of the dark type and (b) a deficiency of allergic conditions, as adrenochrome has an antihistaminic action. Also, it was deduced that (c) an attempt to treat the disease with ascorbic acid and sodium chloride and (d) by reduction of tyrosine and phenylalaine intake would be justified, and that (e) abnormal indole bodies might be expected in the urine.

The data, taken from the records of the Ministry of Pensions and National Insurance, were from 1008 cases of schizophrenia, 5127 of injuries of all types, and 500 of head injuries. Only deductions (a) and (b) above could be investigated on the available evidence. Analysis of the data showed that the schizophrenic series had a highly significant excess of dark-haired men in the age group of 15 to 19 years, and a highly significant deficiency of allergic states, the value of P in both cases being approximately 0.001.

Four possible explanations are discussed. The one thought to be in best agreement with the data is based on the evidence of liver dysfunction in schizophrenics, the paths of adrenalin detoxification in the body, and the excess of dark individuals with trophopathic hepatitis. It is concluded that schizophrenia may be the end result of either hereditary or environmental factors that produce liver damage, this causing abnormally large quantities of adrenalin to be oxidized via adrenochrome to melanin because of the blocking of the metabolic paths through the liver. This view explains the excess of dark types in those 15 to 19 years (hereditary), the presence of other pigmentary types at all ages (environmental), the known liver damage in schizophrenics, and, after a re-examination of Lucy's data on histamine tolerance, the persistence of this tolerance throughout the course of the disease. 22 references. 3 tables.—*Author's abstract.*

For Reference

4. *The Biological Roots of Psychiatry.* R. W. GERARD, Chicago, Ill. Am. J. Psychiat. *112*:81–90, August, 1955.

CLINICAL PSYCHIATRY

5. *Psychopathic Personality.* SIDNEY B. MAUGHS, St. Louis, Mo. Arch. Crim. Psychodynamics *1*:291–325, Spring, 1955.

The author reviews the literature on this subject from 1947 to 1954 and brings his previous reviews up to date. The various studies of the psychopath by means of the electroencephalograph failed to show any electroencephalographic characters or groups of characters that could be specifically related. Instead, the electroencephalogram showed a variety of patterns, all of which we can recognize in a proportion of the normal population. From the point of view of the electroencephalogram, the only differences between a normal and an abnormal population lie in the increased incidence of such patterns among some of the latter. The posterior temporal slow wave focus has seemed the most malignant in its clinical associations. It appears that the presence of abnormal electroencephalographic patterns is a reflection of a maturational defect in cerebral organization, based on a combination of factors.

The wide divergence in articles on this subject at the descriptive level illustrates the need for a more uniform approach to the problem. There has been little, if any, correlation of research and studies and little increase in our understanding of the psychopath. There is a great need for the creation of special facilities for study and research of the psychopath, together with facilities for his confinement and occupation. The psychopath is becoming an increasing problem to the courts, the prisons, and the mental hospitals. Treatment is at present unsatisfactory, and a real, constructive approach to the solution of this personality problem has not yet been found. Recently, the new technique of transorbital lobotomy has been tried without any proven success.

There is an increasing emphasis in the literature on attempts to delineate the psychodynamics of the psychopath. A substitution of the term "anethopath" for that of psychopath and a division of psychopathy into primary and secondary is urged. Primary psychopathy or idiopathy should be applied to those cases—a small group—who do not fit into any of the cardinal reaction types and seem to lack any psychogenetic aspect. Secondary psychopathy should include those cases of psychoses and neuroses that have a strong antisocial or delinquent aspect, and such cases should be classified in their proper group of neurosis or psychosis.

It is hoped that a clearer understanding of psychopathic behavior in the adult will be gained by closer attention to a differential study of psychopathic behavior in infants and children. Treatment of the psychopath is impeded by the hostile attitude of the psychiatrist and of society. There is an increasing amount of evidence suggesting that the causation of psychopathy is to be found in a combination of organic and environmental factors. 52 references.—*Author's abstract.*

6. *Study in Suicidal Attempts.* MURRAY E. FINN, Capt., M.C., Fort Knox, Ky. J. Nerv. & Ment. Dis. *122*:2, February, 1955.

General studies of suicide are briefly described and the problem that suicide poses in its various forms, such as accident proneness, chronic suicidal attempts, and acute suicidal attempts, is emphasized.

The study was conducted on 20 consecutive admissions for suicidal attempts to an Army General Hospital. All of these cases proved to be examples of character and behavior disorder, although psychotic reactions were purposely excluded. The study indicates that people seek suicide because of personality conflicts and psychosexual problems rather than social and economic pressures.

The method of this study consisted of three main categories of investigation: clinical interview, American Red Cross social history, and psychologic testing. No systematic analysis of the psychologic test data was given. The author emphasized that the method of suicide offered little help in the evaluation of the seriousness of attempts. The differentiation between gestures and attempts is extremely difficult because of the factors of alcohol, poor judgment, and immature personalities. Brief summaries of 4 case histories are presented to demonstrate the differences in motivation and personality conflicts found in these patients who made suicidal attempts.

A summary of the personality factors involved in these 20 patients indicated that impulsivity was one of the chief factors and was overt in 18 of the cases and latent in 2 cases. Impulsivity, manifested by impulsive fighting, hot rod driving, and motorcycling, was present in 17 of the 20 cases. Of considerable interest was the presence of significant depression in only 4 of the 20 cases.

The psychodynamics of impulsivity were discussed. Psychodynamically this impulsivity actually served to avoid depression and explained why so little depression was found in these patients.

Depression per se does not mean suicide, and there must be other factors if suicide is to be used as a solution to various problems. Some of these patients were able to impulsively

introject their hostility and make genuine, serious suicidal attempts, despite their narcissistic character orientation.

The elements of spite, a desire to force affection, and narcissistic supplies are extremely important in the character and behavior disorder of one who attempts suicide. Weak ego development and the feeling that "I won't really die" are strong elements in these people. In summary the following psychosexual characteristics were noted: (1) strong dependency demands, (2) strong maternal fixation, (3) weak male identification, and (4) weak deficient psychosexual developments manifested by narcissism, weak object relationships, impulsivity, and poor heterosexual adjustment.

The final note indicated that this study was helpful in differentiating those attempts made by schizophrenics from impulsive suicide attempts made by those suffering from character and behavior disorders.—*Author's abstract.*

7. *A Conceptual Scheme for Psychiatric Syndromes.* GEORGE WINOKUR, St. Louis, Mo. Am. J. Psychotherapy *9*:400–406, July, 1955.

It is desirable to present the psychiatric syndromes in such a way that they can be related to each other and cluster about a basic concept. Such a concept is conflict. It has been shown experimentally and clinically that conflict considerably changes the organism's responses to stimuli. In this scheme, conflict is considered the nuclear concept rather than anxiety; and anxiety is considered a result of conflict. Certain cultures foster particular types of conflicts, but the common denominator in the production of psychiatric syndromes is the conflict itself. The psychiatric syndromes, themselves, may be divided into two groups, one of which may be considered to be protection against conflict and the other, the results of conflict. Among the protections against conflict are hysteria-hypochondriasis, paranoid ideation and paranoia, obsessive-compulsions, and pathologic personality types. The results of conflict include anxiety (which itself may be a step to depression), schizophrenia, and the psychosomatic disorders. These results of conflict are not to be considered in any way valuable to the organism but are rather to be considered an end product of conflict. In other words, they are disintegrative, chaotic processes which are in no way homeostatic. The borderlines of the neurotic-psychotic dichotomy are traversed in this particular scheme by placing hysteria-hypochondriasis and paranoid ideation together as protections against conflict. Both are considered to be evidences of delusional thinking, the difference being in the type of personality present prior to the time that the well-defined clinical picture could be observed. There is much clinical and analogic evidence to warrant considering hysteria-hypochondriasis as being, in reality, a delusional illness, in many ways similar to paranoia. In essence, then, the scheme presented is concerned with a causal relationship for types of symptoms and syndromes. 9 references. 1 figure.—*Author's abstract.*

GERIATRICS

8. *Oral Metrazol Therapy in Senility (A Preliminary Report).* WILLIAM B. SUTER, Mayview, Pa. Dis. Nerv. System *16*:211–217, July, 1955.

Fifteen men, 67 to 83 years old, all of whom showed senile mental disturbances and who

were treated with metrazol, were studied. These patients had all been institutionalized for several years. While all of them showed peripheral arteriosclerosis, hypertension was not marked in any case, and blood pressure readings were normal in several instances. One patient previously had had a cerebral thrombosis, but the resulting hemiplegia had cleared up almost entirely. The usual symptoms noted in these patients were confusion, disorientation, a dull listless attitude, restlessness, and untidiness. They were uncooperative and sometimes quarrelsome, occasionally needing restraint or sedation. Metrazol was given orally in the form of tablets containing 1½ grains each. The usual initial dosage was three tablets given four times daily; after 30 days, two tablets were given four times daily for another 30 days. In 4 patients, the initial dosage was reduced to two tablets four times daily; in 3 of these patients mild convulsive seizures, lasting a few minutes, developed with the larger dosage. All but 3 of the patients treated with metrazol showed definite improvement in personality, becoming pleasant and cooperative; only a few showed definite mental improvement. The one patient who showed no confusion or disorientation recovered and became physically active so that he could be discharged. Nine illustrative cases are reported. From his experience in these cases, the author is of the opinion that two tablets of metrazol four times daily is the most effective dosage; higher doses do not seem to improve the results of treatment. The initial dosage now being employed is two tablets three times a day, which is increased within a few days to two tablets four times a day, if there are no contraindications. Improvement in personality does not usually become evident until after 10 to 14 days of treatment. The period of observation of patients treated with metrazol is not yet sufficient to make it possible to determine how long the improvement will be maintained after treatment is discontinued. 21 references.

9. *Attitude Therapy in Geriatric Ward Psychiatry.* RAPHAEL GINZBERG, Tomah, Wis. J. Am. Geriatrics Soc. 3:445–462, July, 1955.

In contrast to the static approach of the past, an attempt has been made to study the psychoses of advanced life from the viewpoint of dynamic psychiatry. It is felt that not only the organic components, but also their interaction with psychologic and environmental factors have to be taken into consideration in analysis of the total picture. Exclusion of any one of the components may lead to misconceptions. Particular emphasis is placed on disturbances in self-perception with subsequent disorientation in personality concept. It is shown that these types of impairments most probably form the basis of the elderly psychotic's disorientation in his intrapersonal and interpersonal relationships. In discussing psychologic aspects, symptomatology is described in terms of defense reactions developed by the patient to intrinsic and extrinsic factors. It is shown that the bizarre and asocial behavior of an elderly psychotic can easily be misunderstood and its adaptational implications completely overlooked. As a result, the elderly psychotic is rejected rather than encouraged in his attempts to make new adjustments. Turning to environmental factors, it is shown that a negative approach may add to the development of destructive tendencies and that a positive attitude can change the psychotic behavior. It is also shown that psychologic rather than logical methods of communication have to be used, that serious attempts have to be made to understand the symbolism of the elderly psychotic's behavior,

and that emotional channels have to be used in establishing contact with him. A treatment method that is based on the use of both psychologic and environmental tools has been developed and is called attitude therapy. This method takes into account somatic, psychologic, and environmental aspects. It is believed that attitude therapy can serve as the basis for a constructive approach to psychiatric problems in advanced life. 60 references.—*Author's abstract.*

PSYCHIATRY OF CHILDHOOD

10. *Psychological Implications of Breathing Difficulties in Poliomyelitis.* MORTON A. SEIDENFELD, New York, N. Y. Am. J. Orthopsychiat. *25*:788–801, October, 1955.

Breathing difficulties that result from poliomyelitis frequently are associated with psychologic reactions that may be as harmful as the physical traumata. Unfortunately, modern skill and knowledge that has made it possible to overcome many of the physical threats have not kept pace on the psychologic side of the ledger. This appears to be due, in part, to a failure to discern just what destructive psychologic elements result from breathing disturbances.

To throw more light on methods by which the psychologic health of the patient with breathing difficulties can be improved, it is necessary to encourage research that would examine such factors as: (1) the relation of the patient's pre-illness emotional state to the impact of the breathing failure threat; (2) the effect of suboptimal oxygenation, excessive retention of carbon dioxide, and the interference with the normal airway on the psyche; (3) the relation of emotional hyperpnea to the emotional state of the patient; and (4) the psychic stress of the withdrawal of the patient from aids to breathing (weaning effect).

Each of these areas of research is discussed briefly and a number of current researches reviewed. Particular stress is placed upon the relatively untouched sources that seem to offer promise for a better understanding of the patient. The capacity of the patient to tolerate frustration may very well play a deciding role in his ability to accept treatment and in his ultimate recovery. Yet, surprisingly little information exists regarding this characteristic and its meaning in the clinical plan for patient care. Similarly, while much emphasis is placed upon certain aspects of the patient's medical history, relatively little study has been made on the utilization of the patient's emotional history to the best advantage for providing the patient who is a poor emotional risk with an adequate mental hygiene program.

One of our most neglected areas of study thus far is the relationship of the blood-gas metabolism to psychologic adaptation. Where faulty breathing exists, especially when the central control of respiration and the cardiovascular mechanism is concerned, we need far more careful examination of these factors as they influence the homeostatic control of emotions. Obviously there is a potential cyclic factor of altered respiratory status with its resultant alteration of blood and tissue metabolism. This may lead to serious changes in the autonomic nervous system with its attendant effects on the psyche, which in turn again helps to create further disturbances in the central nervous system. Further research done on this complicated process could produce a great deal that would help the clinician protect his patients from undergoing extensions upon his already existing disturbing condition.

Finally, the task of freeing the recovering patient from his dependency upon respiratory aids or equipment merits much closer scrutiny from the psychologic standpoint. The determination of the factors that lead the patient to be psychologically prepared for giving up these devices would help to make this task simpler for both physician and patient. In addition, it should also lead to a reduction in psychologic sequelae following the physical rehabilitation of the patient.

Ample evidence exists for the need for extension of research on breathing difficulties to include careful examination of the many psychologic elements that are involved. 12 references.—*Author's abstract.*

PSYCHIATRY AND GENERAL MEDICINE

11. *Psychosomatic Medicine; Past, Present and Future.* IAGO GALDSTON, New York, N. Y. A. M. A. Arch. Neurol. & Psychiat. *74*:441–450, October, 1955.

Psychosomatic medicine, unlike all other specialties, does not revolve about a technologic skill such as radiology or surgery. It is a singular specialty in that it espouses a distinctive pathologic dynamism. It advances the principle that emotional tensions are often discharged in ways that upset the normal physiologic equilibrium of an organ, thus initiating the somatic changes that produce disease. Its chief concern is with the relationship of emotional tensions to organic and functional disorders.

Present day psychosomatic medicine is historically and actually unique. It constitutes a movement to counterbalance and correct some deeply rooted, erroneous ideas propagated in organicist medicine. Psychosomatic medicine should be holistic in its orientation. Yet, it is still largely committed to the primitive concept of specific etiology and to the "time sequence chain of causality."

The earliest exponents of psychosomatic medicine were the psychoanalysts. Freud was a pioneer in this field and was followed by a number of his associates, Deutsch, Ferenczi, Groddeck, and Jelliffe. Freud's theory of the conversion of repressed emotions into somatic disorders was original and most revolutionary. He considered the syndrome of anxiety neurosis to be the somatic witness of a "psychic repression," while hysteria he held to be the psychic witness of a "somatic repression." At this time the psyche was officially nonexistent. (Pavlov first demonstrated the purely psychologic nature of the neuroses.)

Organicist medicine has long maintained that every disease must have its specific causative factor; psychosomatic medicine has seemingly not challenged this. It has merely added a new factor, the psyche. The psychosomatic patient is all too often shuttled between clinician and psychiatrist. All psychosomatic issues are both clinical and psychologic. The physician or the psychiatrist must carry the responsibility.

The general practitioner should be indoctrinated psychiatrically to treat his own case with full awareness of the psychologic components of the patient's pathology and therapy. If the patient's difficulties become predominantly psychologic, he should be referred to the psychiatrist.

The historical function of the psychosomatic movement is to vitalize medicine (psychiatry no less than clinical medicine) with the holistic and ecological viewpoint. 13 references.—*Author's abstract.*

TREATMENT

a. General Psychiatric Therapy

12. *Occupational Treatment of Chronic Psychotics.* G. M. CARSTAIRS, D. H. CLARK, AND N. O'CONNOR, London, England. Lancet *6898*:1025–1030, November 12, 1955.

This article describes current practice in the rehabilitation of psychotic patients in a number of European centers. In each case, details are given of the material and psychologic setting, the types of occupation offered, and the principles upon which work therapy is based. The profound influence upon contemporary Dutch mental hospital practice of the teachings of Hermann Simon is noted; and Paul Sivadon's notable contribution to French social psychiatry is apparent in the conduct of his unit at Ville-Evrard. It is pointed out that the social-therapeutic principles adopted by those responsible for rehabilitation programs, and in particular the quality of their expectations concerning patients' capabilities, significantly influence the success of their programs. The bearing of social history and of contemporary social and economic circumstances upon rehabilitation policy is discussed, and the relevance of European experience in this field to current and developing British psychiatric practice is indicated. 13 references.—*Author's abstract.*

b. Drug Therapies

13. *Intoxicant Drugs (Mescaline and Lysergic Acid Diethylamide) in Psychotherapy.* WALTER FREDERKING, Hamburg, Germany. J. Nerv. & Ment. Dis. *121*:262–266, March, 1955.

Use has been made of certain drug-induced, dreamlike states as an aid to psychotherapy. Two drugs, mescaline and D-lysergic acid diethylamide (LSD 25), have proved particularly well-suited to this purpose. In his practice, the author has employed mescaline for more than 17 years and LSD 25 for nearly three years. Mescaline is administered intramuscularly in amounts varying between 0.3 and 0.5 Gm. If the amount exceeds 0.3 Gm., two equal doses are given, one hour apart. LSD 25 is given orally in doses of 30 to 60 μg. (maximum dose of 100 μg.), although in some cases 20 to 30 μg. have proved effective. As LSD 25 can be used more often without the risk of harmful effects, it has recently been employed with considerably greater frequency than mescaline. About 200 treatments have been carried out with LSD 25 or mescaline in order to shorten a course of therapy, reactivate a stalled treatment of neurosis, or break down blocks in affect or memory. In almost every instance a psychocathartic effect was noted.

Mescaline exerts a more intense effect than LSD 25 and should therefore be used when it is desirable to obtain the strongest possible emotional upheaval. LSD 25 seems to have a broader spectrum; it frequently causes the patient to re-experience scenes from his early life and can also have a lasting influence on organic-neurotic states, especially in conditions associated with smooth muscle cramps, e.g., chronic constipation and dysmenorrhea. Brief case histories are given to depict the effects of LSD 25 and mescaline. It is considered that in the hands of the experienced psychotherapist, the effects of LSD 25 and mescaline may constitute very valuable therapeutic aids. However, the indications for their use should be prudently selected, and the therapist must have personal experience with the effects of

the drugs so that he may cope with any emotional situation arising from the influence they exert. 17 references.—*Author's abstract.*

14. *Efficacy of Chlorpromazine in Hyperactive Mentally Retarded Children.* H. V. BAIR AND WILLIAM HEROLD, Parsons, Kan. A. M. A. Arch. Neurol. & Psychiat. *74*:363–364, October, 1955.

The authors report the results of chlorpromazine medication in the treatment of the 10 most hyperactive, mentally retarded students at the Parsons State Training School.

A control group was matched with the experimental group according to age, sex, and I.Q. Chlorpromazine was administered to the experimental group (25 mg. orally, three times daily) each day for 60 days. Weekly reports of the students' behavior were submitted by the psychiatric aides, school teachers, therapists, and medical staff. Psychologic tests administered before and after the two month period indicated an average increase in I.Q. of 10.4 points for the experimental group and an increase of 2.5 points for the control group. The weekly reports indicated that 7 students showed vast improvement, 2 improved favorably, and 1 showed no significant change.

The authors attribute the phenomenal change in behavior and I.Q. to the reduction of hyperactivity and anxiety that had prevented the students from functioning at their true level of mental ability. 1 table.—*Author's abstract.*

c. Psychotherapy

15. *Psychotherapy Techniques for Use with Psychotics.* ALBERT ELLIS, New York, N. Y. Am. J. Psychotherapy *9*:452–476, July, 1955.

A comprehensive review was made of the 1950 to 1953 periodical literature on techniques of psychotherapy for use with borderline and psychotic individuals, to complement the previous report on techniques of psychotherapy for use with neurotic or emotionally maladjusted adults (New approaches to psychotherapy techniques, J. Clin. Psychol. Monograph Supplement No. 11, July, 1955).

The number of different techniques of therapy now being advocated for use with psychotic patients is fairly large. In the present survey, 35 different major techniques are listed; under these major headings there are 75 more specific methods of therapy; and under these more specific headings there are several hundred still more specific subheadings.

Although there is considerably more agreement among therapists who treat borderline and psychotic patients than there seems to be among those who treat neurotic individuals, the fact remains that the disagreements among the former therapists are still somewhat startling and wide-ranging. Numerous techniques that one group of therapists dogmatically says should be frequently employed with psychotics are just as dogmatically condemned by some other group of therapists. Which of the techniques advocated are more and which are less valid is completely unclear from the present contradictory state of the literature; and considerable controlled experimentation in the techniques of psychotherapy with psychotics would seem to be in order.

As in the case with techniques of psychotherapy espoused for use with neurotics, there seems to be an increasingly frank avowal of eclecticism in the literature of therapy tech-

niques advocated for use with borderline and psychotic individuals. Therapy with psychotics seems to be more related to practice than to psychodynamic theory; and in practice therapists have apparently found that not one special but a number of different techniques work well with some patients and therapists under certain conditions and work less well with other patients and therapists under other conditions.

While earlier papers on psychotherapeutic technique with psychotics may have stressed expressive-emotive and insight-interpretative methods, recent papers tend to lay greater emphasis on activity-directive and supportive methods. Relationship therapy is particularly stressed today, whereas it was less emphasized several years ago.

Several significant differences appear between the kinds of techniques advocated for use with borderline and psychotic patients and those advocated for use with neurotics. In general, though with some significant exceptions, it is recommended that in the treatment of psychotics, as compared with that of neurotics, (a) classical transference be avoided and interpretation of transference phenomena be quite cautious; (b) the therapeutic relationship, especially in the beginning, be especially positive, warm, and close; (c) free association usually be avoided; (d) the sessions proceed on a face to face, carefully spaced basis; (e) dreams and fantasies be cautiously, if at all, interpreted; (f) probing be avoided; (g) there be a special focussing on reality situations and problems; and (h) the therapist take an unusually active and supportive role. 61 references.—*Author's abstract.*

16. *Psychotherapy of a Mother and Daughter with a Problem of Separation Anxiety.* DAVID B. ROBINSON AND G. M. DUNCAN, Rochester, Minn. Proc. Staff Meet. Mayo Clin. *30*:141–148, April 6, 1955.

This report describes the results of simultaneous psychotherapy by two therapists of mother and daughter who suffered from separation anxiety. The daughter had been kept from school for long periods and had become physically ill as a result of the emotional conflicts. The daughter's problems were finally solved, although there were two relapses. She returned to school and carried on normal activities. The mother, who had herself been dominated by a stepmother for many years, was also improved, gaining insight into her relations with her daughter as an attempt to satisfy her own neurotic needs. In both cases an analysis of the patient's dreams proved of aid in the treatment of the patients. Therapy of the mother is being continued at the time of this report. 1 reference.

17. *Social Class and Duration of Psychotherapy.* STANLEY D. IMBER, EARL H. NASH, JR., AND ANTHONY R. STONE, Baltimore, Md. J. Clin. Psychol. *11*:281–284, July, 1955.

This study of 60 outpatients in group and individual psychotherapy at the Henry Phipps Psychiatric Clinic demonstrated that middle class individuals remain in treatment significantly longer than lower class individuals. The hypothesis that the extent to which patients participate in psychotherapy is not independent of class status was further strengthened by the facts that the training and experience of therapists were held constant and were beyond the minimum level, patients were assigned at random to the therapists, and pressure was exerted on both therapists and patients to maintain their contacts. 7 references. 2 tables.—*Author's abstract.*

18. *An Attitude Technique in the Psychotherapy of Transvestism.* E. L. MARGRETTS. Internat. J. Sexology *8*:172–173, February, 1955.

19. *The Group Psychotherapy Literature—1954.* EMANUEL HALLOWITZ, LESLIE ROSENTHAL, AND TONY HENIG. Internat. J. Group Psychotherapy *5*:299–321, July, 1955.

d. The "Shock" Therapies

20. *An Evaluation of Carbon Dioxide Therapy.* ALBERT A. LAVERNE AND MORRIS HERMAN, New York, N. Y. Am. J. Psychiat. *112*:107–113, August, 1955.

Carbon dioxide inhalation therapy has been in use at Bellevue Psychiatric Hospital for the past three years. During this period, we have treated approximately 200 patients. This is a report on 133 patients whose treatments have been completed and evaluated. We have experimented with different techniques of carbon dioxide therapy and have used these techniques upon a variety of neurotic disorders. We have also applied them to a small group of psychotic disorders and a few spastic neurologic conditions. The techniques employed were exclusively the Meduna and the rapid coma techniques.

Meduna's technique consists of a 30 per cent carbon dioxide in oxygen mixture for 20 to 40 consecutive inhalations, preceded by nitrous oxide anesthesia.

Rapid coma techniques consist of higher concentrations of carbon dioxide (70 to 80 per cent carbon dioxide in oxygen mixture) using single breath technique, single breath technique with voluntary breath holding, multiple breath rapid coma technique, preceded by nitrous oxide anesthesia, multiple breath rapid coma technique, preceded by partial nitrous oxide anesthesia (subcoma).

The majority of the patients in the rapid coma series received multiple breath rapid coma technique preceded by nitrous oxide anesthesia.

A maintenance therapy group consisted of those neurotic and alcoholic patients who improved on the initial full course of treatment but relapsed with a partial or complete return of clinical symptoms after cessation of treatment. These patients were treated weekly with rapid coma technique for an indefinite period.

Treatments were administered three times per week, up to 100 treatments. Patients received up to two years follow-up.

The rationale, according to LaVerne, in rapid coma techniques is that the high concentrations of carbon dioxide introduced suddenly to the respiratory tract and circulation precipitates an intense stress reaction, stimulating the body defenses into action. Furthermore, the physiologic change is so rapid that the resistance of the body tissue to carbon dioxide is minimized.

The use of at least 20 per cent to 30 per cent oxygen in the carbon dioxide mixture of rapid coma techniques is recommended. This is an added safety factor, since the therapeutic difference between 70 per cent to 80 per cent and that of 95 per cent carbon dioxide concentration is insignificant.

In the series of patients thus far studied there was no evidence of increase in intrinsic ventricular irritability. Contraindications are severe hypertension, active pulmonary

tuberculosis, cardiovascular heart disease, severe emphysema, acute allergic respiratory reaction, and respiratory or cardiovascular sensitivity to carbon dioxide and/or nitrous oxide. The therapist should avoid the production of deep or prolonged physiologic levels of coma or convulsions since this increases treatment anxiety and may add to the physical hazard of treatment.

Prior to carbon dioxide therapy, one third of all the patients had received psychiatric treatment unsuccessfully. The clinical results of rapid coma techniques were superior to those achieved by the Meduna technique. Using the Meduna technique, 22 per cent of a neurotic group improved clinically, whereas, 50 per cent improvement in a comparable group was achieved with rapid coma techniques. Forty-seven per cent of a group of 15 obsessive-compulsive neuroses improved clinically when treated with rapid coma technique. Of a group of 24 schizophrenics, 33 per cent improved clinically with rapid coma therapy.

Carbon dioxide therapy with the Meduna technique was ineffective in treatment of a group of 5 cerebral palsy and 2 dystonia musculorum deformans patients. One cerebral palsy patient was treated unsuccessfully with rapid coma.

The diagnosis of treatment anxiety and its management are essential to the armamentarium of the carbon dioxide therapist. The various techniques of carbon dioxide therapy are relatively safe procedures, however, providing the contraindications are observed.

The clinical results achieved with rapid coma in the obsessive-compulsive and other neurotic disorders warrant further investigation. 17 references.—*Author's abstract.*

21. *An Evaluation of Subcoma Insulin Therapy.* DONALD C. GREAVES, PETER F. REGAN, III, AND LOUIS J. WEST, New York, N. Y., and USAF (MC). Am. J. Psychiat. *112*:135–139, August, 1955.

In contrast with the accepted definition and efficacy of coma insulin therapy, the status of subcoma therapy is still not clear. From 1942 to 1952, subcoma insulin therapy at the Payne Whitney Psychiatric Clinic was considered to be that which produced a hypoglycemia sufficient to cause clouded consciousness lasting 45 to 60 minutes but stopping short of coma. It has been used in the treatment of 212 patients during this period. There was improvement in 79.7 per cent of 133 schizophrenic patients, and in 76.9 per cent of 26 patients with affective illnesses. It appears that, in the treatment of certain psychopathologic reactions that occur in schizophrenic and less frequently in manic and depressed patients, subcoma insulin is a useful form of therapy. The psychopathologic reactions that are affected favorably by this treatment are catatonic excitements with marked fear, depression, or elation; acute paranoid reactions with fear, incoherence, elation, or depression; schizophrenic episodes of excessive anxiety; manic excitements with marked anger or sexual excitement; and panic phases in depressive illnesses. Catatonic stupors with marked fear reacted favorably. It should be emphasized that, while many distressing symptoms can be controlled or relieved by insulin, the underlying illness is not necessarily altered. 11 references. 6 tables.—*Author's abstract.*

neurology

CLINICAL NEUROLOGY

22. *Diagnosis and Treatment of Idiopathic Facial Paralysis (Bell's Palsy).* FRED B. MOOR, Los Angeles, Calif. J.A.M.A. *157*:1599–1601, April 30, 1955.

Idiopathic facial paralysis was first described by Sir Charles Bell in 1921. The exact cause is unknown, but among the various suggested etiologic factors are: local chilling, upper respiratory infections, local vasospasm, and a specific viral infection. Several studies have indicated that the paralysis is due to ischemia caused by pressure resulting in peripheral Wallerian degeneration.

The diagnosis is made by the history, the physical examination, and Chronaxie testing. Some physicians use electromyography. Occasionally, consultation with an otolaryngologist or a neurologist may be advisable. The progress of the patient is followed by frequent Chronaxie tests.

Treatment of Bell's palsy should be started as early as possible. It consists of local heat, electric stimulation, massage, exercise, and splinting of the face. Heat in the form of infrared radiation renders the facial muscles more sensitive to the succeeding electric stimulation. Stimulation is done with an interrupted direct current applied if possible three times daily for five minute periods with the current strength at the patient's maximal tolerance. Massage follows and some of it may be done with the thumb or a finger inside the cheek and one finger outside. As soon as voluntary motion begins to return, muscle re-education and exercise are started.

There is a difference of opinion as to the value of splinting of the face. The purpose of splinting is to protect the paralyzed muscles from the pull of gravity and the pull of the contralateral muscles.

The long-range prognosis in Bell's palsy is good, but the speed of recovery depends on early energetic treatment. 15 references.—*Author's abstract.*

23. *Infantile Spastic Hemiplegia.* MEYER A. PERLSTEIN AND PHILIP N. HOOD, Chicago, Ill., and Dallas, Tex. Am. J. Phys. Med. *34*:391–407, June, 1955.

This paper reports on 334 cases of infantile spastic hemiplegics studied with respect to incidence, intelligence, ages of walking, talking words, talking sentences, and birth weight. These patients, representative of heterogeneous geographic and socioeconomic groups, were seen in private practice, in hospital clinics, and in itinerant clinics throughout the Midwest.

The patients ranged in age from 6 months to 26 years, with a mean age of 6.5 years. The ratio of males to females was 4:3. The ratio of Negro to white was the same as that in the general population from which the cases were drawn, 1:6. There was a predominance of Negroes in the group with seizures and in the postnatally acquired group. The ratio of congenital to postnatally acquired cases was 2:1.

The congenital etiologies included dystocia and forceps, 31 per cent; prematurity, 12 per cent; toxemia, 11 per cent; anoxia, 8 per cent; all others, 38 per cent, including 17 per

cent unelicited. The acquired etiologies included: infections, 57 per cent; trauma or vascular accidents, 28 per cent; toxic conditions, 4 per cent; and unknown, 11 per cent.

A total of 270 patients were classified with regard to I.Q. Of these, 28 per cent were mentally defective, i.e., I.Q. below 70. The mean I.Q. of the 173 patients having I.Q. scores was 77. Mental deficiency was definitely associated with the presence of convulsions.

The mean age of walking, as determined by parent interviews, for 170 congenital cases was 23 months; those with seizures walked, on the average, at 27 months. The mean age of talking, i.e., the use of first words, for 156 congenital cases was 22 months; sentences appeared at 31 months of age. A mean birth rate of 6.4 pounds was found in 190 congenital cases. Birth weight was unrelated to the presence of convulsions.

Correlations between several of the measurable variables in this series suggest negligible relationships between birth weight and all other variables. There is a definite but small relationship between first words and intelligence and between first words and walking, while a substantial relationship exists between intelligence and both walking and the use of sentences. 24 references. 11 tables.—*Author's abstract.*

24. *Examination of the Sensory System in Patients After Hemispherectomy.* LYLE A. FRENCH AND DAVID R. JOHNSON, Minneapolis, Minn. Neurol. *5*:390–393, June, 1955.

This report concerns data obtained by doing sensory examinations in a series of 8 patients who had unilateral cerebral hemispherectomies done for the purpose of controlling severe, intractable convulsive seizures. Seven of the patients had infantile type hemiplegias, and in the other patient the hemiplegia developed at the age of 28 and was secondary to scarring that followed the removal of a glioma ten years earlier.

Preoperative examination usually revealed diminished response on the involved side to all modalities of sensory stimulation. It was felt that this diminished response was not decreased sensitivity to stimuli but rather a slowness in perception or recognition of the stimulus.

Postoperative sensory examination revealed a relatively minimal change from the preoperative status. Even in the very early postoperative period both superficial and deep pain could be accurately perceived and located. Light touch was also well defined early, although in this type of sensation there was a more definite difference between the involved and uninvolved side. There seemed to be diminution in the finer discriminative powers of touch perception rather than any actual lack of perception. Even the very lightest touch stimuli with fine hair or cotton could be perceived but stimuli of this sort could not always be differentiated from a coarse touch. Over a period of several months to a year this ability improved but never returned to the preoperative level. During the first three postoperative days, the ability to identify the finger that was touched was lost, but this ability returned to its preoperative level by the seventh to tenth day. The ability to identify the toe that was touched was also temporarily lost but soon returned. Position and vibratory sense did not seem to be altered by hemispherectomy even during the first few days postoperatively. The recognition of relative shapes and weights of objects placed in the hands was diminished during the early postoperative period, seemingly due to lessened motor function in the hand tested, but as the motor control became more adequate so did the ability to accurately

discern the type of article placed in the hand. Two point discrimination was not altered except during the first few days postoperatively when the patients could not distinguish accurately numbers written in the palm. This ability returned gradually and was back to normal by the third week. 4 references.—*Author's abstract.*

ANATOMY AND PHYSIOLOGY OF THE NERVOUS SYSTEM

25. *Myopathies and Functional Disturbances in Muscles.* N. ZEC. Monatschr. f. Psychiat. u. Neurol. *130*:161–185, 1955.

Clinical experience and thorough study of the evidence have led the author to conclude that myopathic disorders are clinical manifestations of some general organic derangement rather than separate nosologic units. He classifies the myopathies into two basic groups. Group 1 includes myotonia congenita (Thomsen), myotonia dystrophica (Steinert-Curschmann), dystrophia musculorum progressiva (Erb), and dystrophia musculorum climacterica, and is concerned with primary disease of higher neurons and centers, the myoneural dysfunction arising when the motor-end plate is freed from the inhibitory action of the upper neurons. Group 2 includes paralysis familiaris periodica, myasthenia gravis pseudoparalytica, and myotonia congenita (Oppenheim). This group also is concerned with derangement of higher centers, but in addition, there is also a primary disorder of the motor-end plate, which has remained at a lower philogenetic level of growth.

All myopathies can be shown to possess this common feature: the clinical manifestations indicate a primary lesion in the central nervous system, located predominantly around the central canal of the spinal cord and the cerebral chambers. Accompanying this are central regulatory and metabolic disturbances and primary dysfunction of the motor-end plate. The result is evidenced by changes in the skeletal muscles.

The central nervous system lesions are presumably due to a primary disturbance of cytodendrogenesis in the areas mentioned previously, the clinical picture depending on the exact site of the lesion. Hence therapy should concentrate on speeding up and regulating the retarded cytodendrogenesis. The author prefers glutamic acid, combined with treatments such as insulin, antibiotics, and the like, which primarily influence the diencephalic hypothalamic region.

CEREBROSPINAL FLUID

26. *A Study of Free Amino Acids in the Human Cerebrospinal Fluid.* JOHN LOGETHETIS, Minneapolis, Minn. Neurology *5*:767–776, November, 1955.

The tedious procedure of paper chromatography of the free amino acids in the human cerebrospinal fluid has been modified to allow analysis of a large number of specimens in a reasonable period of time. This has been accomplished by modifying the desalting apparatus of Consden and developing an apparatus for the automatic spotting of the spinal fluid on the filter paper. Spinal fluids from 17 normal individuals have been analyzed by two dimensional chromatography, and 15 amino acids have been identified and quantitated. These amino acids include aspartic acid, glutamine, gamma-aminobutyric acid, lysine,

phenylalanine, serine, tyrosine, threonine, valine, and leucine. The analysis of 193 spinal fluids from patients with central nervous system disease demonstrated three additional amino acids, namely, proline, histidine, and cystine.

In three disorders, the following statistically significant changes were found: hereditary cerebral ataxia, increased aspartic acid, 2 cases; multiple sclerosis, decreased aspartic acid and tyrosine, 7 cases; presenile psychosis, decreased alanine and glycine, 5 cases. 18 references. 4 figures. 3 tables.—*Author's abstract.*

DEGENERATIVE DISEASES OF THE NERVOUS SYSTEM

27. *Antibrain Antibodies in Multiple Sclerosis.* NAOMI RASKIN, Dorchester, Mass. A.M.A. Arch. Neurol. & Psychiat. *73*:645–655, June, 1955.

The study of antibrain antibodies in the blood of multiple sclerotic patients was based on the premise that the disease is of an allergic nature. The production of acute disseminated encephalomyelitis by injections of nervous tissue emulsions has been reported by several investigators. The histologic picture of allergic encephalomyelitis characterized by vascular and inflammatory reactions was interpreted by some authors as due to immunologic reactions of an allergic type. The etiology of multiple sclerosis is unknown.

The author performed the complement fixation tests using the antigens prepared from the brains of multiple sclerotic patients. The tabulation of findings in 120 multiple sclerotic patients and in control groups showed the difference to be considerable; 83.3 per cent in multiple sclerotic patients and 42.6 per cent in normal, arteriosclerotic, and luetic patients, showing a difference of 40.7 per cent, which is statistically valid. When the serum of a multiple sclerotic patient, giving a strongly positive reaction, was mixed with an equal amount of a normal serum with the same antigen, giving a negative reaction, the positive reaction of the multiple sclerotic serum became much weaker or completely negative. The impression was that the addition of normal sera neutralized the complement fixing bodies in the multiple sclerotic sera, thereby liberating the complement. This led to the treatment of multiple sclerotic patients with blood transfusions, the donors' blood being selected on the basis of this test. The number of the patients treated does not warrant definite conclusions, but the results are encouraging. The methods of treatment and the results will be reported later. 24 references. 1 figure. 7 tables.—*Author's abstract.*

28. *Epidemiologic Investigations of Amyotrophic Lateral Sclerosis (Part I). Familial Aggregations Indicative of Dominant Inheritance (Part II).* LEONARD T. KURLAND AND DONALD W. MULDER, Bethesda, Md., and Rochester, Minn. Neurology *5*:182–196, March, 1955; *5*:249–268, April, 1955.

The etiology of amyotrophic lateral sclerosis or motor system disease is unknown; numerous hypotheses suggesting external factors have been published. It has often been reported that the classic form of the disease is nonhereditary and nonfamilial.

The results of recent and current investigations of the extremely high incidence of amyotrophic lateral sclerosis in the Mariana Islands have suggested a hereditary factor rather than an external causative factor. Among patients with amyotrophic lateral sclerosis on the Mariana Islands of Guam and Rota, a positive family history for amyotrophic lateral

sclerosis is the rule and not the exception. To date, no external etiologic factor has been discovered to explain the high incidence among the Chamorro (native) population of these islands who alone are affected so greatly there. The authors have therefore re-evaluated the possible genetic factors in classic amyotrophic lateral sclerosis. A thorough review of the literature on this subject is made, and additional pedigrees and other data are presented as evidence that amyotrophic lateral sclerosis may occur as a hereditary disease. Several extensive reports of other investigators are cited in which no familial history of the disease is detected.

The familial aggregations in almost all pedigrees are compatible with a dominant form of inheritance, although occasionally an individual who had apparently inherited and transmitted the gene remained free of the trait. The age of onset of the familial cases is essentially the same as that described as the sporadic form. Although among the cases on Guam and in other series of sporadic cases there are more males than females, there is no significant selectivity by sex for the pedigrees included here.

The authors emphasize that the majority of cases of amyotrophic lateral sclerosis observed in the United States fail to provide a history of a similar disorder in other family members. It is their impression that amyotrophic lateral sclerosis does occur as a hereditary disease. Whether the basic etiology of the sporadic cases differs from those that are on a hereditary basis remains to be seen. 61 references. 20 figures. 1 table.—*Author's abstract.*

ELECTROENCEPHALOGRAPHY

29. *The Electroencephalogram of Aged Patients with Cardiac and Cerebral Vascular Disease.* W. D. OBRIST AND L. F. BISSELL, Hartford, Conn., and Ann Arbor, Mich. J. Gerontol. *10*:315–330, July, 1955.

Previous work has shown that the electroencephalogram undergoes characteristic changes in old age. In the present experiment, an attempt was made to determine the relation between these changes and the occurrence of clinical heart disease and cerebral vascular disease. Electroencephalographic studies were done on 60 aged men, including 21 normal controls, 20 with clinical evidence of heart disease, 14 with heart disease and a cerebral vascular accident, and 5 with evidence of a cerebral vascular accident only.

All of the 21 normal control subjects had an alpha rhythm greater than 8.5 cycles/second, which is within normal limits for young adults. The mean alpha frequency for the group was 9.4 cycles/second. Delta activity was recorded in only 1 case. In the 20 patients with heart disease, a slow alpha rhythm of less than 8.5 cycles/second was recorded in 12 subjects, with a mean alpha frequency for the group of 8.3 cycles/second. Delta activity appeared in 8 cases. Altogether, 70 per cent of the cardiac group had either a slow alpha rhythm, delta activity, or both. Tracings of the 14 subjects with both cardiac and cerebral vascular disease differed from normal, but to a lesser extent than those with cardiac disease only. Forty-three per cent of these cases had either a slow alpha rhythm and/or delta activity. All of the 5 patients with cerebral vascular disease only showed one or both abnormalities. When the subjects in the three groups with cardiovascular disease were combined, a mean alpha frequency of 8.5 cycles/second was obtained, as compared with 9.4 cycles/second for the normal group. While only 5 per cent of the normal group showed delta activity,

about one third of the other subjects showed such activity. The slowing of the electroencephalogram was related to the presence of abnormality in the electrocardiogram. The mean alpha frequency of patients with normal electrocardiograms was 9.3 cycles/second, while the mean frequency of the group with abnormal electrocardiograms was only 8.3 cycles/second. There was a similar relationship between the presence of cardiomegaly and the slowing of the alpha frequency.

It was concluded that slowing of the alpha rhythm and appearance of delta wave activity in the electroencephalograms of aged persons are correlated with the presence of cardiovascular disease. However, a causal relationship does not necessarily exist between cardiovascular disease and the electroencephalogram. Further work is needed to determine the exact inter-relationship between cardiovascular disease, cerebral blood flow and metabolism, and the electroencephalogram of the aged person. 29 references. 3 figures. 3 tables.—*Author's abstract.*

30. *Differentiation Between Anxiety and Depression by the Photically Activated Electroencephalogram.* CHARLES SHAGASS, Montreal, Canada. Am. J. Psychiat. *112*:41-46, July, 1955.

The purpose of this study was to test the hypothesis that anxiety and depression are characterized by differences in cerebral responsiveness, demonstrable in the photically activated electroencephalogram. In the method used, the amplitude of the parieto-occipital response to intermittent photic stimulation, at flash rates of 10 and 15 per seconds, was measured. The relative response at 15, as compared with 10 flashes per second, was determined (15:10 ratio).

Subjects for the study were taken from a total sample of more than 400 consecutive admissions to the psychiatric wards of a general hospital. Selection was limited to patients with no past history of convulsive manifestations, electroconvulsive therapy, alcoholism, or myoclonic responses to photic stimulation. No case was used unless two psychiatrists agreed that there were adequate case history criteria to warrant a definite diagnostic statement. In addition, 29 nonpatient control subjects were studied. The present analysis was primarily based on patients with the following disorders: anxiety states, 31; psychoneuroses with a mixture of anxiety and depression (mainly neurotic depressions), 30; depressions, 38; and schizophrenia, 35.

There was a significant difference of driving response between the sexes, with females showing a greater response at all frequencies. The 15:10 response ratio was significantly higher in patients with anxiety states than in patients with depressions, while control subjects and paranoid schizophrenics had intermediate ratios. Serial studies in a single control subject indicated that the driving response was labile and fluctuated in relation to feeling state. The direction of these fluctuations was as expected from the group differences demonstrated between anxiety and depression.

It was concluded that the results of this exploratory study supported the hypothesis that the photically activated electroencephalogram is quantitatively different in different emotional states. Further research along these lines was considered indicated. The possible significance of the experimental approach as a way of bringing together data from clinical and animal neurophysiologic research was pointed out.

INFECTIOUS AND TOXIC DISEASES OF THE NERVOUS SYSTEM

31. *Pathological Changes in the Nervous System from Occupational Causes.* CYRIL B. COURVILLE, Los Angeles, Calif. Bull. Los Angeles Neurol. Soc. *20*:41–61, June, 1955.

Occupational hazards may entail the application of force, exposure to certain physical agents, inhalation of asphyxiant gases, the contact of irritant substances with the skin or mucous membranes, or the ultimate absorption of these or other toxic substances into the circulation with damage to the viscera and the nervous system. Such hazards to the brain usually involve either mechanical force or exposure to noxious substances. In this category are infectious or parasitic lesions of the brain, alterations incident to abnormal atmospheric pressure, and exposure to the extremes of heat and cold or to high voltage electricity.

From an analysis of the gross and microscopic findings in the cases of occupational disease, it appears that the characteristic changes are due to circulatory changes, anoxemia, and direct effects of poison on the cell. The circulatory effects cannot always be separated from those incident to anoxemia, of which it may be an integral part. The congestion complex is most characteristically found in heat or sunstroke or poisoning with methyl alcohol, tetraethyl lead, manganese, vanadium, barium, arsenic, hydrocyanic acid, the alcohols, the aliphatic esters, certain of the organic solvents, and the asphyxiant gases. The edema complex is most characteristically seen in acute intoxication with lead, nickel carbonyl, manganese, the arsenicals, phosgene, fluorine, hydrocyanic acid, and the alcohols, notably methyl and ethyl.

Regardless of the mechanism by which a given noxious agent reaches the nervous system, it is evident that it exerts a specific action on certain groups of nerve cells or local structures. These local responses stand out in contrast to the general effects of the agent on the cerebral cortex, resulting in mental confusion, delirium, or stupor. However, both general and specific effects may occur and can often be distinguished one from another. One of the most typical and well-defined of the specific effects is that manifested by certain heavy metals (lead) and metaloids (arsenic) on the peripheral nerves. Carbon monoxide, carbon disulfide, thallium, and gasoline are also known to produce typical peripheral neuropathy. The cerebral cortex is very commonly affected by solvent poisons, as illustrated by the well-known effect on the cortical nerve cells by such poisons as the asphyxiant gases, notably carbon monoxide and nitrous oxide, certain metals such as lead, mercury, manganese, thallium, zinc, vanadium, and antimony, the alcohols, some halogens (i.e., bromine), and some chemical compounds, such as carbon disulfide and the halogenated hydrocarbons. The cerebral centrum may be altered either as an acute effect of congestion and hemorrhage or a chronic degenerative process. The first situation is exemplified by the occurrence of petechial hemorrhages after exposure to the asphyxiant gases, phosphorus, mercury, arsenic (more particularly the organic compounds), nickel carbonyl, and the cyanides. Chronic degenerative changes are also found as residuals of chronic intoxication with the cyanides, carbon monoxide, nitrous oxide, and carbon disulfide. The cerebellum seems less often specifically altered by noxious substances, although this organ frequently suffers as a part of the general toxic state. There is some evidence to suggest that this organ is more particularly injured by such substances as carbon disulfide, tetraethyl lead, mercury, thallium, and possibly cadmium as well.

The gross and microscopic changes of the cerebral lesions include circulatory changes, hemorrhage as a toxic lesion, cerebral edema as an indirect circulatory effect of certain toxic agents on the brain, and cerebral ischemia incident to vasospasm. Changes in the blood vessels, including endothelial proliferation with new capillary formation and the ultimate development of a dense vascular scar in the intermediate layer of the cerebral cortex, hyalinization of the small arterioles, and calcification of the muscle coat of the arterioles of the lenticular nucleus or in areas of central necrosis in cases of carbon monoxide poisoning, constitute an integral part of the terminal picture. Architectural alterations of the leptomeninges and brain substance, whether cortical, ganglionic, or central, focal infarctions of the white matter, central necrosis of the lenticular nucleus, especially of the globus pallidus, may also be present and at times form a characteristic pattern. Alterations in the parenchyma both of the nerve cells (acute, subacute, and chronic) and the nerve fibers (fragmentation of the myelin sheaths with the formation of myelin balls and their transformation into free fat) are particularly significant in view of neurologic symptoms. Alterations in the interstitial elements are usually secondary. 40 references. 10 figures.—*Author's abstract.*

INTRACRANIAL TUMORS

32. *Multiple Intracranial Expanding Lesions of Diverse Origin.* EMANUEL H. FEIRING, New York, N. Y. Neurology *5*:535–541, August, 1955.

Three cases of multiple intracranial expanding lesions of different histologic nature are reported. In 1, a sphenoid wing meningioma and a frontal glioblastoma multiforme were present; in another, a glioblastoma multiforme was found in the parietal region at the exact site of an abscess removed several years previously; in the third case, there existed a frontal meningioma and a glioblastoma multiforme in the contralateral frontal region. The presence of multiple lesions was recognized and verified during life in each case. The existence of more than one intracranial mass may be suspected at times on the basis of the clinical data. Failure to improve postoperatively as anticipated or an unexpected recurrence of symptoms following the removal of a benign growth should suggest the possibility of another independent lesion. 13 references. 8 figures.—*Author's abstract.*

NEUROPATHOLOGY

33. *Congenital Hydrocephalus Due to Atresia of the Foramen of Magendie.* JAMES B. GIBSON, Belfast, Ireland. J. Neuropath. & Exper. Neurol. *14*:244–262, July, 1955.

This rare type of hydrocephalus is characterized by dilatation of the fourth ventricle in a special form. Instead of being enclosed by brain tissue, the ventricle is roofed caudally by an extensive membrane. Anomalies of the cerebellar inferior vermis are consistently present. Published cases are reviewed and 2 new ones are reported and described in detail.

The first case, a 12 year old boy, is an example of the most marked form of the condition in which the ventricle is dilated into a cystlike structure in the posterior fossa. In addition, the foramina of Luschka were closed. The abnormal roof of the fourth ventricle is described; large parts of it were neural in character, and the elements that compose it were derived from the structures apparently missing from the inferior vermis.

In the second case, where the deformity was less severe, the foramina of Luschka were patent. In this case, the atretic foramen of Magendie was closed by an ependymal diverticulum comparable to that found throughout life in some mammals and to that appearing in the human fetus at about the 100 mm. stage, but disappearing normally before the 150 mm. stage. The atresia of the foramen was thus a persistent fetal condition. The associated deformities of the inferior vermis can be related directly to this atresia, for they are exactly those that would be expected where hydrocephalic dilatation of the fourth ventricle began about the 150 mm. stage. These deformities can be understood by considering the stage of development reached by the affected parts at that time.

It is held that the failure of the foramen to perforate is the crucial malformation; there is no evidence of incomplete closure of the neural tube or of rachischisis.

A subarachnoid space was present in the first case, in which all the efferent foramina from the fourth ventricle were closed, and so it appeared that the development of this space did not depend on an outflow of cerebral spinal fluid from these foramina. In the second case, ectopic glia was found in the subarachnoid space around the medulla.

Differential diagnosis and radiologic signs are briefly considered. 43 references. 11 figures. —*Author's abstract.*

TREATMENT

34. *WIN 8077 in Treatment of Myasthenia Gravis.* ROBERT S. SCHWAB, CLARE K. MARSHALL, AND WILLIAM TIMBERLAKE, Boston, Mass. J.A.M.A. *158*:625–628, June 25, 1955.

Mysuran, WIN 8077, in the treatment of myasthenia gravis is effective in a large percentage of patients. It has a longer duration of action and a higher threshold for side effects than neostigmine. Seventy-five patients ranging in age from 15 to 74 years were treated with mysuran. Fifty-nine are still taking the drug. Some found the effect roughly equivalent to that of neostigmine, others found it definitely superior; 17 preferred some neostigmine or mestinon with the mysuran.

Mysuran is somewhat stronger and has approximately twice the duration of action of neostigmine. This was particularly helpful to 10 severely ill patients who previously had to have their sleep interrupted for medication. This disagreeable feature was eliminated with the new medicine.

Some patients did well on 2 to 4 mg. per dose, others required 50 to 75 mg. per dose. Several patients reacted unfavorably to the drug with the typical symptoms of overdosage caused by an anticholinergic substance. Therapy with mysuran was stopped, and they were returned to their previous medication. It is advised to start with 0.5 ml. of a syrup containing 12.5 mg. of mysuran in 4 ml. to determine the patient's sensitivity, and gradually increase the dose with syrup, only changing to tablets when the optimum dose has been established. At the present time, parenteral use has had inadequate trial and therefore is not recommended at all. The side effects of mysuran are similar to those of neostigmine. In patients with tracheotomies, the large doses of mysuran that caused increased secretions were almost entirely due to salivation, with little, if any, increase in tracheal and bronchial secretions. This is of vital benefit in the management of patients in respirators. In muscarinic effect, mysuran seems usually to stimulate the upper intestinal tract, so that nausea

and vomiting are more prominent than with neostigmine. Cold perspiration, small pupils, excessive salivation, and increase in weakness of voluntary muscles are signs of overdosage. Intravenously given, atropine is the antidote of choice.

The side effects first appear very close to the toxic level, so that there is a narrower margin of warning before serious toxic effects occur than is the case with other antimyasthenic drugs. With less warning, great variation in the patient's requirement, and prolonged action of the drug, much greater care and supervision is mandatory. 8 references. 2 figures. —*Author's abstract.*

BOOK REVIEWS

Textbook of Occupational Therapy. EAMON N. M. O'SULLIVAN, B.A., M.B., D.P.M. New York, Philosophical Library, 1955. Pp. 319. Price $10.00.

This book deals in part with administrative procedures, organizing and staffing of a department of occupational therapy and its influence in a hospital setting, and the relationships among the individual staff members in the hospital. The sections and units of the occupational therapy department have been divided into handicrafts, recreational therapy, re-educational, and a commercial section. Two chapters are devoted to the psychologic analysis of mental diseases and mental states, although there are many references in the book to disabilities other than psychiatric. The author has gone into craft analysis in detail, selecting several specific crafts, such as woodcraft and weaving.

Little mention is made of the interpersonal relationships between the occupational therapy staff and the patients, but emphasis is placed on interstaff rapport and on the use of specific crafts in their relation to patients' diagnoses.—*Arvilla D. Merrill.*

The Present Status of the Problems of Release of Patients from Mental Hospitals. WINFRED OVERHOLSER, M.D., SC.D. Psychiatric Quarterly, Vol. 29, Pp. 372–380, July, 1955.

The author reviews the development of the State's duty toward the mentally ill, with particular reference to the acts of patients released from mental hospitals.

"There is a heavy responsibility upon the hospitals to see to it that the community is not exposed to unnecessary risks of violence and injury, but there is, at the same time, a duty to treat and care for patients and to restore them to a useful life in the community so far as possible. At some point along the line, a balance between these two contending interests must be struck. Certainly, psychiatrists will see to it that they do not knowingly subject the public to unnecessary risks (actually psychiatrists do not!), but on the other hand public clamor cannot be allowed to exert an inimical and retarding effect on the treatment of our patients."

NOTES AND ANNOUNCEMENTS

The Bio-Science Information Exchange.

The Bio-Sciences Information Exchange is a noteworthy service which has been made available to all workers engaged in biologic research activities, including neurologic,

psychiatric, and psychologic research. Originally organized as the Medical Sciences Information Exchange of the National Research Council, it was enlarged in 1953 to incorporate the psychological as well as the basic biological sciences. This enlargement of its functions and organization resulted in its transfer to the Smithsonian Institution.

The purpose of the Exchange, as described by its Director, Dr. Stella Leche Deignan, is to serve as a clearinghouse for research activities. Its primary function is to coordinate information relative to the amounts and sources of support of investigators, institutions, and geographical areas as well as the amounts and sources of support of broad and specific fields of research. The material gathered enables the Exchange to serve as a clearinghouse for private investigators as well as research institutions. It is this latter function which is of particular interest to the readers of this journal.

The principal data of the Exchange consist of brief statements of current research problems which have been submitted by investigators and organizations. Investigators are protected from premature publication of their work by the clear understanding that their material will not be used in any publication without their special and explicit permission. They have been very cooperative in providing adequate summaries of proposed and current projects. These summaries describe the design and object of investigations and are not intended to provide results. Since few investigators have refused to furnish summaries, the files of the Exchange are quite complete. A detailed subject index has been developed which includes all projects for which summaries have been received. By means of this index the Exchange professional staff, consisting of competent individuals in the biologic, psychologic and medical fields, is in a position to place investigators in contact with others with similar interests by providing them with summary statements of pertinent research projects. An investigator contemplating a new project may obtain from the Exchange, without charge, the most complete and most recent available information as to work currently in progress relative to his particular problem. The value of such a service may readily be appreciated.

Dr. Deignan has pointed out, "The Exchange differs from a reference library in that it does not refer an investigator to a publication, but enables him to contact directly those with immediate and similar interests whose works might not yet be concluded or published." The investigator may thereby become aware of unpublished results and be spared the repetition of similar experiments. The index maintained by the Exchange is so constructed that its professional staff can extract with considerable precision the particular area of work in which the investigator is interested and preclude forwarding to him a large number of remotely connected summaries.

The Exchange is also in a position to provide information concerning the interests and policies of national granting agencies which may be of assistance to investigators seeking sources of support. The names of many local and frequently not well known foundations are also on file and have been listed by State in the belief that such lists may assist research institutions in their search for local sources of funds. Individual investigators and institutions are invited to make use of the facilities of the Exchange, the present address of which is 1113 Dupont Building, Washington 6, D. C. Investigating agencies, research institutions, and private investigators are also invited to submit research summary statements on appropriate forms which may be obtained from the Bio-Sciences Information Exchange.

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&

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